ARCHIVES OF SURGERY

VOLUME 43 JULY 1941 NUMBER 1

COPYRIGHT, 1941, BY THE AMERICAN MEDICAL ASSOCIATION

PHYSIOLOGIC EFFECTS OF HIGH CONCENTRATIONS OF OXYGEN IN EXPERIMENTAL SECONDARY SHOCK

HARRY A. DAVIS, M.D.

NEW ORLEANS

Despite the widespread use of oxygen therapy for clinical shock, few studies have been made of the effect of high concentrations of oxygen in experimental shock. The rationale of the method is based on the fall of oxygen consumption associated with hemorrhagic and traumatic shock, which was first pointed out by Aub and Cunningham [1] and which has since been confirmed by many other workers. The present report concerns a series of experiments undertaken to investigate the physiologic action of high concentrations of oxygen on normal control animals and experimental animals in which secondary shock had been produced.

MATERIALS AND METHODS

Dogs weighing from 10 to 25 pounds (4.5 to 11.3 Kg.) were kept under light anesthesia produced by intravenous injection of pentobarbital sodium in doses of ¼ grain (0.015 Gm.) per kilogram of body weight. The arterial blood pressure was recorded with a mercury manometer by means of a cannula inserted in the right carotid artery. Studies made on blood withdrawn from the femoral artery and vein consisted of red and white cell counts, determination of the level of hemoglobin (Sahli), hematocrit readings and estimation of the values for sugar, nonprotein nitrogen, sodium chloride, carbon dioxide–combining power and oxygen content. The blood for the gas determinations was withdrawn under oil.

Hemorrhagic shock was produced by bleeding the animal through the cannula inserted into the carotid artery. It was thus possible to study the response to administration of oxygen in shock associated with hemodilution. Shock associated with hemoconcentration was produced by the method described by me,[2] which consists of injection of

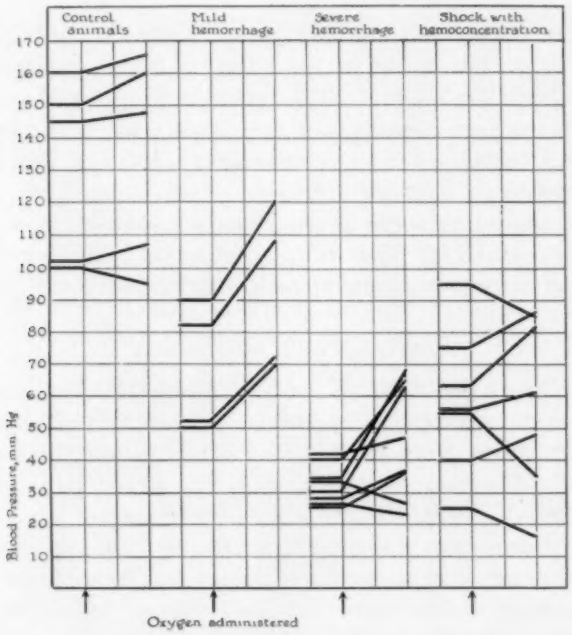
From the Department of Surgery of the School of Medicine of Louisiana State University.

1. Aub, J. C., and Cunningham, T. D.: Studies in Experimental Traumatic Shock: II. The Oxygen Content of the Blood, Am. J. Physiol. **54**:408-415, 1920.

2. Davis, H. A.: Acute Circulatory Failure (Shock) Following Subcutaneous Injection of Hypertonic Sodium Chloride Solution, Proc. Soc. Exper. Biol. & Med. **43**:354-357, 1940.

25 per cent sodium chloride solution subcutaneously in doses of 25 cc. per kilogram of body weight. The shock produced by this procedure closely resembles that which follows trauma, but the effects are more uniform and more constant. After the injection of hypertonic sodium chloride solution the blood pressure does not fall to the shock level until three or four hours has elapsed.

Oxygen was administered in amounts of 1,000 cc. per minute for fifteen minutes by a tube inserted into the trachea through a tracheotomy opening. It was humidified by passage through water, and the flow was regulated by means of a flow meter.



Influence of administration of oxygen on blood pressure.

PHYSIOLOGIC EFFECTS OF OXYGEN IN NORMAL ANIMALS

Blood Pressure.—In the majority of instances the administration of oxygen to normal animals produced no changes in the blood pressure. Occasionally a slight fall occurred, and a rise of 2 to 5 mm. of mercury was sometimes observed (chart).

Pulse Rate.—A slowing of the pulse rate, which varied from 4 to 20 beats per minute, was frequently observed following the administration of oxygen. The mechanism of the diminution is not clear at this time.

Blood Changes.—Determinations of the hemoglobin content of the blood by the Sahli method showed slight increases, varying from 1 to 3 per cent, following the administration of oxygen. Hematocrit determinations revealed similar slight increases in the amount of the cellular elements. The red blood cells were also slightly increased in number, the increases being in the neighborhood of 200,000 to 300,000 per cubic millimeter. The increases in the amount of hemoglobin and in the number of red blood cells were not great, but their uniform occurrence after the administration of oxygen to normal animals suggests some definite

TABLE 1.—*Influence of Administration of Oxygen on Blood of Control Animals*

Dog	Red Blood Cells (in Millions) per Cu. Mm.		Hemoglobin, per Cent		Hematocrit, per Cent		White Blood Cells, per Cu. Mm.	
	Before Oxygen	After Oxygen	Before Oxygen	After Oxygen	Before Oxygen	After Oxygen	Before Oxygen	After Oxygen
5	5.65	6.3	78.5	81	52	54	6,150	6,100
1	4.68	4.98	55.8	58	29	30	16,600	13,000
2	5.91	5.8	84.5	88	37.5	37	11,500	10,050
3	5.04	6.21	79	90	45	46	7,225	4,800
4	6.23	6.72	100	103	54.9	56	5,750	4,800

TABLE 2.—*Influence of Administration of Oxygen on Blood Gases of Control Animals*

Dog	CO_2–Combining Power (Arterial Blood), Volumes %			Oxygen Content (Arterial Blood), Volumes %		
	Before Administration	Immediately After Administration	15 Minutes After Administration	Before Administration	Immediately After Administration	15 Minutes After Administration
4	20.3	20	18.2	19.6	22.8	21.37
3	44	29	25	21.2	25.5	24.4
2	55	54	51	18.5	20	21
5	29.5	26	18	19.71	22.59	19.49
1	54	30	47	19.4	27.15	18.15
18	35.5	32.7	36.8	17.76	19.53	18.58

relation between them. The white blood cells were definitely reduced in number, the reduction varying from 10 to 30 per cent of the initial number. The decrease in the number of leukocytes was thus relatively greater than the increase in the number of red blood cells (table 1).

Little change was observed in the blood sugar, the nonprotein nitrogen of the blood and the blood chlorides (determined as sodium chloride) after the administration of oxygen. The carbon dioxide–combining power of the blood was definitely decreased, and the decrease was maintained for as long as twenty minutes after the administration of oxygen was discontinued (table 2). The data available thus demonstrate the strange fact that the administration of oxygen causes an increase in the amount of carbon dioxide in the blood. Although this phenomenon,

which has been observed by other workers, has been attributed to defects in the respiratory apparatus, certain other possibilities suggest themselves. It may be due to the stimulation of tissue metabolism resulting from the increased oxygen content of the blood. It may be a homeostatic response designed to increase the utilization by the tissues of the increased amount of oxygen in the blood, an explanation which would seem to be supported by the work of Bohr and his associates,[3] who showed that the dissociation of oxygen from oxyhemoglobin takes place more rapidly in the presence of increased amounts of carbon dioxide in the blood.

The oxygen content of the blood was increased after the administration of oxygen, the increases varying from 10 to 50 per cent above the initial level. The increase was not maintained, however, as was the alteration in the carbon dioxide–combining power, and within fifteen to twenty minutes after the oxygen had been discontinued the oxygen content of the blood had returned to the original level (table 2).

Before proceeding further it is necessary to consider the effects in these control animals of the administration of oxygen on the coefficient of oxygen utilization (C. O. U.), which is the amount of oxygen utilized by an organ or tissue in any given period. It is obtained by subtracting the venous oxygen content from the arterial oxygen content and dividing the result by the arterial oxygen content, the oxygen content being calculated as volumes per cent. The formula may be represented simply by

$$\frac{A_o - V_o}{A_o} \times 100 = \text{C. O. U. (in volumes of oxygen per cent)}$$

An increase in the coefficient of oxygen utilization indicates an increased utilization of oxygen by the tissues, due either to an increase in their rate of metabolism or to a decrease in the rate of blood flow through the area under consideration, which would allow more oxygen to diffuse from the blood to the tissues. Conversely, a decrease in the coefficient indicates a decreased utilization of oxygen by the tissues, due either to a diminution in the rate of metabolic activity of the tissue or to an increase in the rate of blood flow through the area, which would permit less oxygen to be given off from the blood to the tissues.

The administration of oxygen to control animals produces a decrease in the coefficient of oxygen utilization, which, if one assumes that no alteration occurs in the ability of the tissues to utilize oxygen, must be the result of an increase in the rate of blood flow (table 3).

3. Bohr, C.; Hasselbalch, C. B. K., and Krogh, A.: Ueber den Einfluss der Kohlensäurespannung auf die Sauerstoffaufnahme im Blute, Zentralbl. f. Physiol. **17**:661-664, 1903. Hasselbalch, C. B. K., and Krogh, A.: Ueber einen in biologischer Beziehung wichtigen Einfluss, den die Kohlensäurespannung des Blutes auf dessen Sauerstoffbindung übt, Skandinav. Arch. f. Physiol. **16**:402-412, 1904.

TABLE 3.—*Influence of Administration of Oxygen on Oxygen Content of Blood and Coefficient of Oxygen Utilization (C. O. U.) in Shock*

	O_2 Content, Volumes % Arterial	Venous	A-V Difference	C. O. U., Volumes %	O_2 Content, Volumes % Arterial	Venous	A-V Difference	C. O. U., Volumes %	O_2 Content, Volumes % Arterial	Venous	A-V Difference	C. O. U., Volumes %
	Initial				After O_2				15 minutes after O_2			
Control	17.76	12.43	5.43	30.5	19.53	13.65	5.88	30.1	18.58	13.24	5.34	28.7
	Initial				After O_2				15 minutes after O_2			
Control	17.96	13.56	4.4	24.4	20.61	15.76	4.85	23.5	17.02	13.01	4.01	23.5
	Initial				After hemorrhage				After O_2			
Mild hemorrhage	19.98	10.58	9.1	45.5	16.43	9.34	7.09	43.1	18.2	11.99	6.21	34.1
	Initial				After hemorrhage				After O_2			
Mild hemorrhage	23.32	17.92	5.4	23.1	19.06	14.73	4.33	22.7	22.4	17.54	4.86	21.6
	Initial				After hemorrhage				After O_2			
Severe hemorrhage	16.2	12.15	4.05	25.0	12.77	9.06	3.71	29.05	14.13	11.67	2.46	17.4
	Initial				After hemorrhage				After O_2			
Severe hemorrhage	18.79	11.72	7.07	37.6	15.45	8.88	6.55	42.4	17.21	9.41	7.8	45.3
	Initial				After shock				After O_2			
Shock with hemoconcentration	16.76	12.32	4.44	26.4	18.09	11.98	6.11	33.7	19.42	11.3	8.12	41.8
	Initial				After shock				After O_2			
Shock with hemoconcentration	14.64	12.32	2.32	15.8	18.04	14.96	3.08	17.0	19.53	15.17	4.36	22.3

PHYSIOLOGIC EFFECTS OF OXYGEN IN HEMORRHAGIC SHOCK

Mild Hemorrhagic Shock.—The administration of oxygen to animals in which the blood pressure had been lowered to 50 to 90 mm. of mercury by graded hemorrhage caused a moderate rise of blood pressure, varying from 10 to 30 mm. (chart). The pulse rate, which had been accelerated by the bleeding, became slightly slower after the administration of oxygen. No constant alteration was observed in the blood constituents, but the carbon dioxide–combining power of the blood was diminished and the oxygen content slightly increased.

The carbon dioxide–combining power of the blood, which had diminished after the production of hemorrhage, was still further decreased by the administration of oxygen. A slight increase in the oxygen content of the blood was observed in some animals after the production of hemorrhage, but in most instances the oxygen content of both the arterial and the venous blood diminished slightly. The administration of oxygen resulted in increases in the oxygen content averaging 1.7 volumes per cent.

TABLE 4.—*Influence of Administration of Oxygen on Blood Gases in Hemorrhagic Shock*

	CO_2-Combining Power, Volumes % (Arterial Blood)			Oxygen Content, Volumes % (Arterial Blood)		
Dog	Initial	After Hemorrhage	After Oxygen	Initial	After Hemorrhage	After Oxygen
8	26	16	13.3	18.76	11.51	12.4
11	27.2	19.4	9	18.79	15.43	17.21
16	32	21	14	16.2	10.91	12.5
23	21	13.5	9.5	19.98	16.43	18.2

Hemorrhage sufficient to produce a mild degree of circulatory failure resulted in a diminution of the coefficient of oxygen utilization, which, assuming that the metabolic needs of the tissues did not vary over the experimental period, suggests the occurrence of an increased rate of blood flow. The administration of oxygen resulted in a further diminution of the coefficient (table 3). It seems reasonable to assume, therefore, that oxygen accelerates the rate of blood flow in animals suffering from mild circulatory failure due to hemorrhage.

Severe Hemorrhagic Shock.—Examination of the blood of animals in which the blood pressure had been lowered to 15 to 40 mm. of mercury by bleedings repeated until the pressure showed no tendency to rise above these levels revealed the usual changes associated with severe hemorrhage. The carbon dioxide–combining power was markedly lowered, especially when the shock had persisted for some time, and the oxygen content of both the arterial and the venous blood was greatly diminished (table 4). The coefficient of oxygen utilization was

increased, which, again assuming that the metabolic requirements of the tissues were not altered during the experimental period, suggests the occurrence of a diminished rate of blood flow (table 3). It is clear, therefore, that oxygen utilization differs in mild and in severe hemorrhagic shock.

When oxygen was administered to animals in severe hemorrhagic shock, an increase in blood pressure usually occurred, varying from 5 to 30 mm. of mercury (chart). The effect was more pronounced when the state of shock had not been allowed to exist too long (more than thirty minutes). In some animals a further fall of blood pressure resulted from the administration of oxygen. It was noted that the continuous administration of oxygen to animals with blood pressures varying from 15 to 25 mm. of mercury was capable of prolonging their lives. The maintenance value of continued administration of oxygen in the presence of low levels of blood pressure due to hemorrhage, as will be emphasized later, may have some clinical significance.

The administration of oxygen causes some slowing of the heart rate in cases of severe hemorrhagic shock. When the blood pressure is greatly lowered and the heart rate slow and irregular it may cause an improvement in the pulse rate parallel with the rise in blood pressure.

Both the carbon dioxide–combining power and the oxygen content of the blood were altered by the administration of oxygen, though no constant effects on the blood constituents were noted. The carbon dioxide–combining power, which had fallen after repeated bleedings, was still further reduced by the administration of oxygen. The oxygen content of the blood was moderately increased, the average increase being 1.5 volumes per cent (table 4). The response of the coefficient of oxygen utilization to oxygen varied. When oxygen was administered after the period of lowest blood pressure had existed for less than thirty minutes the coefficient was decreased, which suggests that the rate of blood flow increased through the tissue under consideration. When, however, the period of low blood pressure exceeded thirty minutes, the coefficient was increased by the administration of oxygen, which may indicate a decrease in the rate of blood flow and the consequent escape of more oxygen from the blood to the tissues (table 3). It is evident, therefore, that the degree and duration of the reduction of the blood pressure in cases of severe hemorrhagic shock have an important bearing on the response to administration of oxygen.

The question arises as to the effect on the oxyhemoglobin dissociation curve of the extreme dilution of the blood which occurs in hemorrhage. The increase in the coefficient of oxygen utilization in the presence of severe hemorrhagic shock suggests that the dissociation of oxyhemoglobin is not decreased. Richards and Strauss [4] observed that

4. Richards, D. W., and Strauss, M. L.: Oxy-Hemoglobin Dissociation Curves of Whole Blood in Anemia, J. Clin. Investigation **4**:105-126, 1927.

the oxyhemoglobin dissociation curves for whole blood in the presence of severe primary and secondary anemias were similar to those for normal blood when the *p*H was normal or slightly lowered. Since in cases of severe hemorrhage acidosis is present and the *p*H of the blood is lowered, the conditions would seem favorable for the normal dissociation of oxyhemoglobin.

PHYSIOLOGIC EFFECTS OF OXYGEN IN SHOCK ASSOCIATED WITH HEMOCONCENTRATION

In animals in which shock associated with hemoconcentration was produced by the injection of hypertonic salt solution, the blood pressure was maintained at the initial level for three or four hours. During this period the blood exhibited profound changes. Within an hour after the injection an increasing hemoconcentration was observed. The blood sugar and the nonprotein nitrogen rose above normal levels. The

TABLE 5.—*Influence of Administration of Oxygen on Blood Gases in Shock Associated with Hemoconcentration*

	CO_2-Combining Power, Volumes % (Arterial Blood)			Oxygen Content, Volumes % (Arterial Blood)		
Dog	Initial	After Shock	After Administration of Oxygen	Initial	After Shock	After Administration of Oxygen
7	34.1	17.1	14	18.6	16.09	23.69
19	35.6	14.5	11.4	21.26	10.63	17.27
20	20.9	14	11.6	32.5	21.76	24.2
21	38.0	13.72	7.32	18.7	16.09	19.42
22	36	28.5	15.3	14.61	12.43	16.87

carbon dioxide–combining power showed a marked diminution, and the oxygen content, despite an occasional temporary rise, progressively diminished, reaching very low levels before death (table 5). The coefficient of oxygen utilization was definitely increased, which if it is assumed that the oxygen requirements of the tissues did not alter during the experimental period, can be attributed to a reduction in the rate of blood flow (table 3). Such a reduction would permit the passage of larger amounts of oxygen from the blood to the tissues.

Oxygen was administered after the blood pressure, at the end of the stationary period, had fallen to levels between 55 and 95 mm. of mercury. The results varied. A rise of blood pressure, varying from 10 to 19 mm. of mercury, occurred in some animals. In others the blood pressure remained unaffected, and in still others it was actually lowered, the decreases varying from 5 to 20 mm. of mercury (chart). The effects of oxygen on the pulse rate were so varied that conclusions are not justified.

The constituents of the blood, other than the carbon dioxide–combining power and the oxygen content, were not uniformly affected

by the administration of oxygen. The carbon dioxide–combining power, which was already diminished as the result of the injection of hypertonic salt solution, showed a further decrease when oxygen was administered (table 5). The oxygen content was definitely augmented, the increase in the arterial blood averaging 4.8 volumes per cent, which represents increases ranging to 30 per cent of the initial levels. Examination of the blood fifteen minutes after the administration of oxygen was discontinued revealed that, although the oxygen content had dropped, it was still higher than it had been prior to the administration of oxygen. A definite increase in the coefficient of oxygen utilization occurred, which, if it is assumed that the oxygen needs of the tissues had not altered during the experimental period, suggests that a diminution of the rate of blood flow occurs as the result of the administration of oxygen (table 3).

At this point the question arises as to why the oxygen content of the blood falls in this form of shock, in spite of the increase in the amount of hemoglobin per cubic centimeter of blood. That the decrease is not directly due to some inability of the concentrated blood to absorb oxygen is shown by the greater increase in its oxygen content as compared with the increase in oxygen in normal blood under the same circumstances. It is possible that the diffusion of oxygen through the lungs to the blood may be less efficient when the blood is concentrated. This theory is supported by the work of Ray, Thomas and Strong,[5] who found in lung perfusion experiments that increasing the number of red blood cells in the perfusion fluid resulted in inadequate oxygenation of the blood. These authors offered four possible explanatory factors: (1) reduction of the rate of diffusion of oxygen through the alveolar capillaries in the presence of hemoconcentration; (2) the longer time taken for complete equilibration of concentrated blood, as determined from dissociation curves; (3) dilatation of the capillaries of the lung in the presence of hemoconcentration, which means that the oxygen must travel an increased distance to complete the process of oxygenation, and (4) distention of the alveolar capillaries, which diminishes the size of the alveoli and, as a result, the amount of air available for oxygen diffusion.

The possibility must also be considered that the threshold of concentrated blood is higher than that of normal blood, so that higher pressures of oxygen than normally exist in air would be required to raise the oxygen content. Finally, the reduction in the rate of blood flow will diminish the oxygen content of the blood, since less blood will pass through the lung for aeration during any given period of time.

5. Ray, G. B.; Thomas, C. I., and Strong, J. E.: The Oxygenation of Concentrated Versus Normal Bloods, J. Clin. Investigation **12**:1051-1062, 1933.

COMMENT

An analysis of the results of this investigation reveals that the power of the blood to absorb oxygen in the presence of shock varies according to the type of shock. In the control animals the administration of oxygen resulted in an average increase of 3.5 volumes per cent of oxygen in the arterial blood. In animals with mild hemorrhagic shock the increase was 1.7 volumes per cent, and in animals with severe hemorrhagic shock it was only 1.5 volumes per cent. In animals with shock associated with hemoconcentration, however, the increase was 4.8 volumes per cent. The decrease in the amount of hemoglobin associated with hemorrhage is probably the chief factor in the reduction of oxygen absorption. It has been pointed out that in the presence of mild hemorrhagic shock the coefficient of oxygen utilization is diminished; this is in agreement with the work of Grant,[6] who showed that therapeutic bleedings of patients suffering from cardiac failure resulted in a diminution of oxygen utilization. The effect of oxygen on the coefficient of oxygen utilization for animals suffering from mild hemorrhagic shock is to reduce still further the level of oxygen utilization, probably as the result of an increase in the rate of blood flow. In this respect my own work substantiates the observations of Wood, Mason and Blalock.[7]

In contrast to the differences in the oxygen content of the blood in the presence of various types of shock, there is a striking similarity between the coefficient of oxygen utilization in cases of severe hemorrhagic shock and in cases of shock associated with hemoconcentration. Such a similarity would seem to indicate that some fundamental process is common to both, in spite of the fact that with one type of shock there is an extreme dilution of the blood, and with the other, an extreme degree of concentration. This common process is probably the marked reduction in the rate of blood flow, an assumption which is further justified by the similarity of the effect of administration of oxygen on the coefficient of oxygen utilization in the two types of shock. The administration of oxygen in these experiments resulted in an increase in the oxygen content of both the arterial and the venous blood and in an augmentation of the utilization of oxygen, but there did not seem to be a definite relation between these effects and the effect of administration of oxygen on the blood pressure. It was frequently observed that the administration of oxygen increased both the amount of oxygen absorbed and the coefficient of oxygen utilization but had

6. Grant, S. B.: Changes in the Blood Oxygen Following Therapeutic Bleeding in Cardiac Patients, J. Lab. & Clin. Med. **9**:160-165, 1923.

7. Wood, G. O.; Mason, M. F., and Blalock, A.: Studies on the Effects of the Inhalation of a High Concentration of Oxygen in Experimental Shock, Surgery **8**:247-256, 1940.

no effect on the falling blood pressure, particularly in cases of shock associated with hemoconcentration. The probable explanation of the continued fall of blood pressure in spite of the increase in absorption and utilization of oxygen is that in animals suffering from shock with hemoconcentration the reduction of blood volume by the passage of a plasma-like fluid into the site of injection was continuous until death.

The behavior of the arteriovenous oxygen difference in response to the administration of oxygen varies with the type of shock. In the normal animal the administration of oxygen results in an increase in the arteriovenous oxygen difference (table 3). Hemorrhage, whether mild or severe, causes a reduction, which is usually followed by a further fall if oxygen is administered. An increase in the arteriovenous oxygen difference, however, occurs after the administration of oxygen in instances in which the blood pressure has remained at a low level for a prolonged period and in which there has been an increase in the coefficient of oxygen utilization. An increase in the arteriovenous oxygen difference always occurs in shock accompanied with hemoconcentration and is further increased by the administration of oxygen (table 3).

The effect of oxygen is predominantly vasopressor (chart), in that a rise of blood pressure occurs not only in normal animals but in animals suffering from mild or severe hemorrhage or from shock associated with hemoconcentration. The mechanism of the increase is not completely known, but three possible causes present themselves: (1) an increase in cardiac output; (2) a direct or indirect action on the blood vessels, resulting in vasoconstriction, and (3) an increase in blood volume.

Wood and his co-workers [7] found an increase in the cardiac output after the administration of oxygen in the animals in which this was searched for. In lower animals the inhalation of oxygen results in a contraction of the cerebral blood vessels (Tinel; [8] Schmidt [9]). In man also administration of oxygen produces contraction of the cerebral blood vessels (Lennox and Gibbs [10]) and of the retinal blood vessels (Cusick and others [11]). Indirect evidence would therefore suggest that the

8. Tinel, J.: Régulation de la circulation cérébrale à l'inhalation d'oxygène, Compt. rend. Soc. de biol. **96**:665, 1927.

9. Schmidt, C. F.: The Intrinsic Regulation of the Circulation in the Hypothalamus of the Cat, Am. J. Physiol. **110**:137-152, 1934.

10. Lennox, W. G., and Gibbs, E. L.: The Blood Flow in the Brain and the Leg of Man and the Changes Induced by Alteration of Blood Gases, J. Clin. Investigation **11**:1155-1177, 1932.

11. Cusick, P. L.; Benson, O. O., and Boothby, W. M.: Effect of Anoxia and of High Concentrations of Oxygen on the Retinal Vessels: Preliminary Report, Proc. Staff Meet., Mayo Clin. **15**:500-502, 1940.

pressor activity of oxygen is due to at least two factors, one of which is an increase in cardiac output and the other of which is vasoconstriction.

It will be noted that a vasodepressor response to oxygen was more often seen in animals suffering from massive hemorrhage or from shock associated with hemoconcentration than in normal animals or animals suffering from mild hemorrhage (chart).

At present no data obtained by direct experiments are available as to the influence of oxygen on blood volume. Indirect evidence based on changes in the erythrocyte count and in the hemoglobin and hematocrit readings (table 1) does not suggest that an increase in blood volume follows the inhalation of oxygen in normal animals.

The close relation which was observed between oxygen utilization and blood pressure in animals with severe hemorrhagic shock can be explained by the fact that in these animals no further diminution of blood volume was taking place; the increase of oxygen utilization was therefore reflected in a rise of blood pressure. In several animals with severe hemorrhagic shock whose blood pressures were stabilized in the neighborhood of 25 to 30 mm. of mercury it was observed that continuous administration of oxygen was able to prevent a further drop of blood pressure for several hours. It would seem that under such conditions oxygen is capable of preventing further falls in blood pressure provided that the reduction of blood volume has ceased, though ordinarily animals with blood pressures maintained at these levels die within an hour.

SUMMARY AND CONCLUSIONS

An investigation has been carried out concerning the effects of the administration of oxygen on normal animals and on animals suffering from hemorrhagic shock and from shock associated with hemoconcentration.

The results suggest that administration of oxygen is most efficacious when the reduction of the blood volume has ceased and is least efficacious in shock associated with a continued decrease in the blood volume.

The best results were obtained in animals with mild hemorrhagic shock. Good results were also obtained in animals with severe hemorrhagic shock, but the administration of oxygen was of relatively little value for animals with shock associated with hemoconcentration, probably because the reduction in the blood volume continued.

The effects of the administration of oxygen on oxygen absorption and oxygen utilization are discussed.

Although the results of this investigation cannot be applied *in toto* to shock in man, certain clinical considerations are implicit in it:

1. It seems clear that the administration of oxygen should be regarded merely as a subsidiary form of treatment in cases of shock.

2. The best results are obtained before a considerable diminution in the blood volume has occurred, regardless of whether shock is associated with hemodilution or with hemoconcentration.

3. The administration of oxygen is useless in cases of severe shock if the blood volume continues to decrease. If the blood volume is low but no further decrease occurs, oxygen may have the effect of stabilizing the low blood pressure and preventing its further fall until other forms of therapy are available.

RESECTION OF THE LIVER FOR HEPATOMA

RICHARD H. WALLACE, M.D.
BOSTON

Primary cancer of the liver in the absence of cirrhosis is unusual, and most reports on the subject are from autopsy observations. Hepatoma in an otherwise normal liver may originate in the parenchymatous liver cells or in the intrahepatic bile ducts. This tumor may grow slowly for years before it spreads through hepatic vessels or metastasizes widely. The symptoms usually are mild indigestion or disturbance caused by the size and weight of the tumor, but massive intra-abdominal hemorrhage has occurred.

Few surgeons have reported on resectable hepatoma. In the literature I have been able to find 29 cases, in 7 of which the tumor originated in the right lobe. Of the 23 patients who survived operation, there was no later report of 3, and 8 died of recurrence. A primary hepatoma may be encapsulated and appear benign; it may grow very slowly; it may have areas of cystic degeneration, or it may be associated with hemorrhage which goes on to calcification. However, hepatoma originating either in the liver cells or in the bile ducts is at least potentially malignant and should be removed, together with a margin of normal liver tissue. In only 2 cases in which the patients died of recurrence has mention been made of resection through normal tissue, whereas such resection is described in the majority of cases in which the patient remained free of disease. Twelve patients have been reported alive and well after operation—5 for less than two years, 3 for three years and 4 for longer than five years.

Keen [1] in 1892 first reported a successful resection of the liver for solitary adenoma. The tumor was described as measuring 3½ inches (8.8 cm.) vertically and the same transversely, with a breadth of 2½ inches (7.3 cm.) where it joined the liver, at the extreme right border. It contained numerous small cystic areas and was removed by a cautery and finger nail dissection. Four large veins were ligated, and the stump of the liver resembled that of an amputation, having two flaps, which were approximated with deep sutures. The pathologic diagnosis was

---

From the Pondville Hospital at Norfolk, Massachusetts Department of Public Health.

1. Keen, W. W.: On Resection of the Liver with a Report of a Successful Case of Resection of Adenoma of the Bile Ducts, Boston M. & S. J. **126**:405-409, 1892.

adenoma of the bile ducts. Later, Keen [2] reported the patient well without recurrence eight years after resection, and, in addition, he reported a case of resection of an adenoma of the left lobe.

Yeomans [3] in 1915 reviewed the literature on resected primary cancer of the liver and reported 16 operative cases, in 6 of which the patient was alive and well from three to seven years after removal of the tumor.

Wright [4] in 1923 reported from England the removal of a hepatoma the size of a Jaffa orange from the right lobe of the liver of a man of 60. The tumor was excised through normal liver with a knife, and the raw area was packed with gauze. The patient was alive without recurrence thirty-one months later. Wright wrote: "I think the simple method of cutting boldly through liver tissue is quite safe."

Turner [5] in 1921 resected a portion of the right lobe of the liver, together with the gallbladder, of a boy of 13 who had a liver cell hepatoma. He first placed deep sutures in normal liver tissue and then with a sharp knife excised the tumor with a V excision. Several large vessels were clamped and tied, and the raw edges were approximated. The pathologic diagnosis was liver cell tumor of hepatic origin, with the cells secreting bile and no bile ducts in the substance of the tumor. The specimen is preserved in the Museum of the University of Durham College of Medicine in England. The boy was well one year and ten months after operation.

Schrager [6] in 1937 presented a paper discussing the pathologic picture and differential diagnosis of adenoma of the liver and reported successful excision of a grapefruit-sized adenoma on a small pedicle in close relation to the suspensory ligament.

Charache [7] in 1939 published a comprehensive review of the subject of primary carcinoma of the liver, summarizing 14 cases in which operation on the liver had been performed since the last report of Yeomans. To the cases previously cited he added 7 of resection for hepatoma with operative survival.

---

2. Keen, W. W.: Report of a Case of Resection of the Liver for the Removal of Neoplasm, Ann. Surg. **30**:267-283, 1899.

3. Yeomans, F. C.: Primary Carcinoma of the Liver, J. A. M. A. **64**:1301-1306 (April 17) 1915.

4. Wright, G.: Case Report, Proc. Roy. Soc. Med. (Sect. Surg.) **16**:56-58, 1923.

5. Turner, G. G.: A Case in Which an Adenoma Weighing Two Pounds, Three Ounces Was Successfully Removed from the Liver, Proc. Roy. Soc. Med. (Sect. Surg.) **16**:43-56, 1923.

6. Schrager, V. L.: Surgical Aspects of Adenoma of the Liver, Ann. Surg. **105**:33-43, 1937.

7. Charache, H.: Primary Carcinoma of the Liver, Am. J. Surg. **43**:96-105, 1939.

Tinker and Tinker [8] in 1939 presented an excellent review of the subject of hepatic resection in general and reported the results of experimental study. They pointed out factors favorable to safe resection of the liver:

1. The lobes and subdivisions of the liver are supplied by independent arteries; so one section can be removed without injury to the remaining sections.

2. Anastamoses between blood vessels of different lobes of the liver are free, insuring adequate circulation if a section is cut off from its normal blood supply.

3. Regeneration after removal of liver substance is rapid and quite complete.

Mann [9] recently reported the results of animal experiments, emphasizing the importance of the portal circulation for restoration of the liver after partial removal.

In the following case the patient was alive and well more than five years after hepatectomy for a grapefruit-sized hepatic cell hepatoma of the right lobe.

REPORT OF A CASE

A 23 year old housewife was admitted to the Pondville Hospital on June 14, 1935.

Chief Complaint.—A lump in the right side had been present for four years.

Present Illness.—Four years before her admission to the hospital the patient first noticed a dragging sensation in her right side and soon discovered a lump. She consulted a physician, who told her that she had a floating kidney and recommended no treatment. Shortly thereafter she had a single episode of pain in the right upper quadrant of the abdomen and stated that she was yellow for a few days. She had had no similar pain since but had avoided fatty foods because they gave her indigestion. The tumor had gradually increased in size; the dragging sensation had become more bothersome; she had become easily fatigued, and she had been unable to carry on her ordinary housework. Several physicians were consulted, and she had been told at various times that she had a floating kidney, a cyst, a renal tumor and an ovarian cyst.

Past History.—The patient was born in Italy, where as a child she had frequent contacts with dogs. She had had malaria twice.

Marital History.—The patient was married at the age of 15 and had three normal children.

Physical Examination.—The patient was pale; a grapefruit-sized tumor was visible opposite the umbilicus, on the right side. When she stood it descended to the right lower abdominal quadrant. The tumor was smooth, rather firm, nontender and freely movable but could not be moved into the pelvis. It was easily palpated with one hand in the costovertebral angle.

---

8. Tinker, M. B., and Tinker, M. B., Jr.: Resection of the Liver: Conditions Favorable for Operation; Methods; Experimental Studies, J. A. M. A. **112**:2006-2008 (May 20) 1939.

9. Mann, F. C.: The Portal Circulation and Restoration of the Liver After Partial Removal, Surgery **8**:225-238, 1940.

The heart and lungs were normal. The blood pressure was 126 systolic and 84 diastolic. Pelvic and rectal examination gave negative results.

Laboratory Data.—The red blood cell count was 3,010,000 and the white blood cell count was 8,400 per cubic millimeter. The value for hemoglobin was 60 per cent. The differential count was normal.

The Hinton reaction was negative. The value for nonprotein nitrogen was 30 mg. per hundred cubic centimeters. Renal function was normal. The urine was normal.

Roentgen Data.—The Graham test revealed that the gallbladder was not visible after administration of the dye.

A pyelogram showed the renal shadows normal in position and outline. After the injection of an opaque medium the renal pelves and calices were well demonstrated and were normal.

Examination of the colon by means of a barium sulfate enema showed that the colon filled readily as far back as the cecum. There was definite displacement

Fig. 1.—Presenting surface of the tumor, which measured 15 by 13 by 5 cm.

of the ascending colon by a tumor mass situated lateral and anterior to it. The mass seemed closely related to the colon, as it moved with the colon when the patient was put in the upright position. There was also slight displacement of the terminal loop of ileum to the midline and downward by the mass, which appeared to have a smooth, rounded contour, The pattern of the mucous membrane was entirely normal in the vicinity of the tumor. This definitely ruled out the possibility of intrinsic tumor of the colon in this case. Films were taken of the tumor mass. In both the anteroposterior and the lateral view a soft tissue tumor about 10 cm. in outline could be identified. In its upper portion a ring of calcium about 4 cm. in diameter was seen. It was situated in the anterior portion of the abdomen, on the right side.

Operation (R. H. W., June 21).—Ether anesthesia was used.

The abdomen was opened through a right paramedian incision. The tumor was dark and firm, with large dilated vessels over it. It involved the right lobe of the liver, and its weight had stretched out the remaining normal liver tissue to a breadth and thickness of 8 cm. There was no liver tissue under the left side

of the diaphragm, as the tumor had rotated the whole liver so that the left margin of the left lobe rested to the right of the midline. An elongated gallbladder containing stones extended over the under surface of the tumor. The other contents of the abdomen were normal. The cystic duct and artery were clamped, cut and tied separately, and the gallbladder was not dissected from the tumor. After an overlapping series of mattress sutures had been placed through normal liver tissue the tumor, with the gallbladder attached, was removed by a wedge-shaped incision with a sharp knife through normal liver tissue. The mattress sutures were

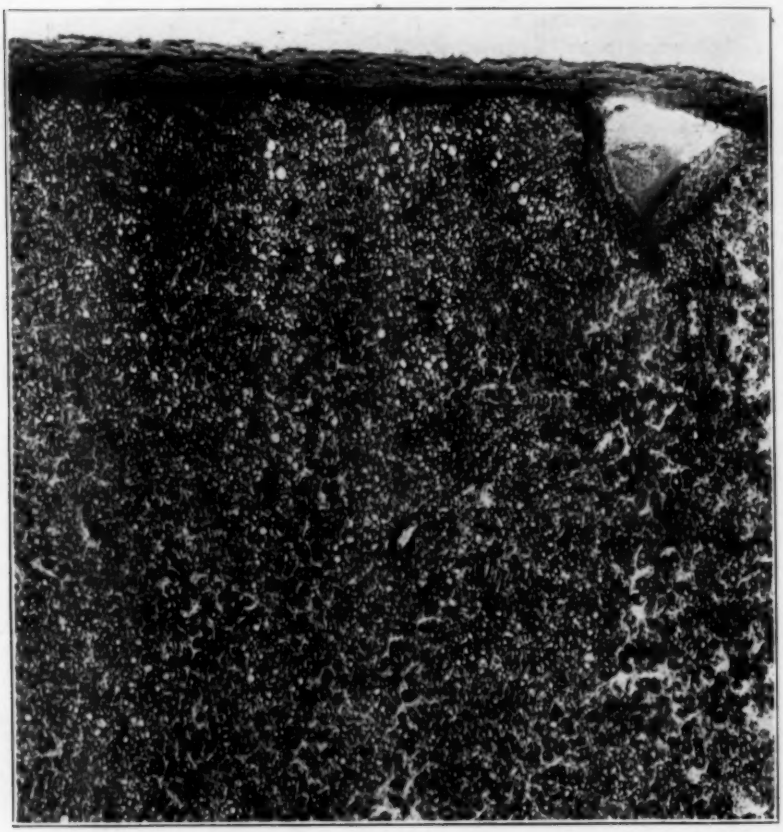


Fig. 2.—Low power photomicrograph of tumor tissue.

tied, and the raw edges were sutured with a running stitch, leaving a dry field. The abdomen was closed with one cigaret wick to Morrison's pouch.

Progress.—There was a small amount of bile-stained serum for three days. The patient had a "flat chart" after seventy-two hours and an uncomplicated convalescence.

Pathologic Report (Dr. Shields Warren).—The specimen was a mass of deep yellowish brown, moderately firm tissue measuring 15 by 13 by 5 cm., It was

covered by thin, smooth serosa traced by large and prominent vessels. The surface was irregularly bossed, with a more elevated, pedunculated portion which was likewise covered by serosa except over one mass measuring 6 by 4.5 by 1 cm. Close to this was the gallbladder, its serosal surface continuous with that over the tumor. It contained a large stone of the mixed type measuring 3 by 1.5 by 0.5 cm. and one smaller stone. The bile was viscid and yellow. The mucosa was reddened. On section, the tumor presented a yellow-brown appearance; here and there it was irregularly streaked with deep red. Close to the broad base of

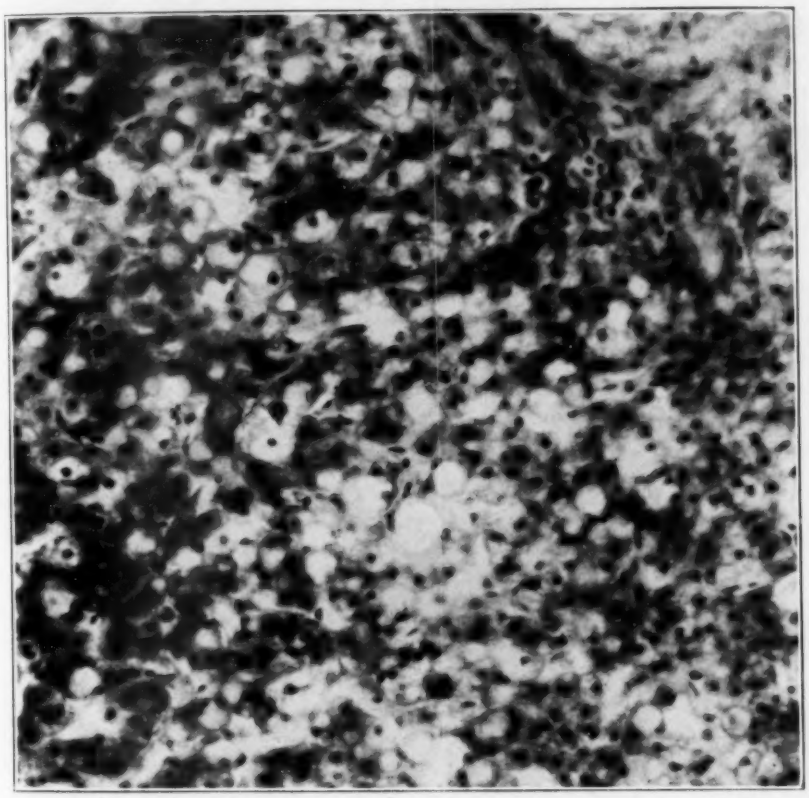


Fig. 3.—High power photomicrograph of tumor tissue.

the fibrous hilus was a focus 3.5 cm. in diameter of reddish, firm clot within a wall 1 mm. thick, white and dense, with calcified foci. A similar but smaller focus (1.7 cm. in diameter) was also present. The tumor substance was soft and friable.

Microscopic Description: The tissue was composed of cords of cells recognizable as hepatic cells, arranged in lobular formation about central veins. The cells were slightly smaller than normal liver cells, and their nuclei were more compact. The portal spaces contained an artery and a vein, but no bile ducts could be made out.

The diagnosis was hepatoma.

Follow-Up.—The patient has reported regularly to the clinic and was last seen by me on July 12, 1940, more than five years after partial hepatectomy. She stated that she had been perfectly well, with no more weakness, discomfort or indigestion. Since two months after her operation she had been able to care for her home and family, which she had previously been unable to do. Examination revealed her to be healthy appearing, with a solid scar and no sign of recurrence.

SUMMARY AND CONCLUSIONS

A patient with a large solitary liver cell hepatoma is reported alive and well more than five years after partial resection of the liver.

Solitary hepatoma, even though it may appear encapsulated and benign, is malignant and should be removed, together with a margin of normal liver tissue.

264 Beacon Street.

SKIN TRANSPLANTATION BY INJECTION

ITS EFFECT ON HEALING OF GRANULATING WOUNDS

C. GLENN BARBER, M.D.
CLEVELAND

The injection of minute particles of dermal tissue suspended in saline solution beneath the surface of a granulating wound to stimulate healing of an indolent raw surface is at present an unusual mode of skin transplantation. The method is not new,[1] but it is scarcely known and seldom used. During the past fifteen years I have observed beneficial results from its use in numerous orthopedic cases when attempts at skin grafting by the usual methods either had failed or were deemed inadvisable.

The value of skin transplantation as a therapeutic measure for the replacement of lost surface tissue cannot be discussed at length in such a communication as this; neither do the details in the technic of application or the advantages and disadvantages of the several methods now in common use require extended exposition. Before entering into a detailed discussion of the method proposed in this paper, however, it would seem fitting at least to mention the important contributions which have chronicled the attempts to standardize the technic of various methods.

HISTORICAL REVIEW

Tissue transplantation has been shown by the literature of antiquity to have been practiced on a highly developed scale by the ancients. The Egyptians as far back as 3500 B. C. practiced the grafting of tissue, as is shown by the Ebert papyrus (1500 B. C.); the Sacred Vedas, or holy books, of equal antiquity, reveal that flap and grafting operations were well known to the ancient Hindus. The Kornas, a caste of Hindu potters, made use of grafts from the gluteal region. The skin of the buttocks of the donor was beaten with a wooden shoe until it was red before the graft was taken.[2]

From the Department of Surgery, Division of Orthopaedics, St. Vincent Charity Hospital.

1. Pels-Leusden: Ueber abnorme Epithelisierung und traumatische Epithelcysten, Deutsche med. Wchnschr. **31**:1340, 1905.

2. (*a*) Fomon, S.: The Surgery of Injury and Plastic Repair, Baltimore, William Wood & Company, 1939. (*b*) Jones, L. P.: The History and Technique of Skin Grafting, West Virginia M. J. **6**:5, 1911.

The art spread [3] from Egypt and India to the southern parts of Asia, to Persia and Arabia and thence to Greece; afterward, according to Carpue,[3b] it passed to Calabria and from there to other parts of Italy. Celsus (53 B. C. to 7 A. D.) wrote with authority in his "De medicina" on the transplantation of tissues from one part of the body to another. Galen (130 to 210 A. D.) gave minute instructions regarding the repair of defects about the ears, nose and mouth. He advised the removal of all scar tissue and the approximation of wound margins by sutures and by sticking plaster.[4]

During the Dark Ages what was known of tissue transplantation was forgotten, and it was not until the nineteenth century that the art of free tissue transplantation was resurrected.

In 1869, Reverdin,[5] a Swiss surgeon, working in Guyon's service in the Hospital Necker, Paris, France, demonstrated the possibility of successfully transplanting pieces of epidermis to a granulating area, and on this demonstration are based the theory and practice of skin grafting as it is done today. His clinical application was prompted by his observation of islands of epithelium in the midst of granulations. As he had accepted Billroth's explanation that these islands arose from proliferation either of the epithelium of the cutaneous glands or of scattered bits of the germinal layer of epidermis, it occurred to Reverdin that epithelization of granulating surfaces might be expedited by the artificial implantation of small islands of epithelium. Accordingly, he took the opportunity to demonstrate the practicability of the procedure for a patient who had lost the skin of his thumb. With the point of a lancet he cut from the patient's arm two morsels of epidermis, each about 1 mm. square, transplanted them onto the granulating surface and immobilized them by means of a strip of lead plaster. Within a few days these transplants proliferated to the margins of the wound. The procedure he termed *"greffe epidermique."*

On Dec. 8, 1869, Reverdin [5] made his momentous report before the Société Impériale de Chirurgie, in which report he described the procedure in detail. All of his colleagues except Guyon, his teacher, and Marc See regarded the procedure with such skepticism that the significance of the discovery and its surgical possibilities went unrecognized

3. (*a*) Davis, J. S.: Plastic Surgery, Philadelphia, P. Blakiston's Son & Co., 1919. (*b*) Carpue, J. C.: An Account of Two Successful Operations for Restoring a Lost Nose, London, Longman, Hurst, Rees, Orme & Brown, 1816. (*c*) Cotton, F. J., and Ehrenfried, A.: Reverdin and Other Methods of Skin Grafting, Boston M. & S. J. **161**:911, 1909.

4. Fomon.[2a] Cotton and Ehrenfried.[3c]

5. Reverdin, J. L.: Greffe épidermique, Bull. Soc. de chir. de Paris **10**:493, 1869.

for the time being. Pollock,[6] of London, England, however, learning of Reverdin's discovery, put it into practice in May 1870, and so spectacular were the results that they immediately aroused the enthusiasm of the medical fraternity of London.

Successful results were soon reported in Ireland, Scotland,[7] America,[8] Germany,[9] Russia[10] and Italy.[11] In 1872 Reverdin[12] again reported, this time on his experience in 50 personal cases and on the results obtained by other surgeons with this type of graft.

As experience grew, much information regarding these grafts was accumulated by various surgeons, and objection was made, as was pointed out by Thiersch[13] in 1872, on the grounds that healing was slow; that the new tissue was little more than a cicatrix; that the grafts were subject to contraction, and that the result was unsightly. In an endeavor to overcome these disadvantages, Thiersch popularized a method which has since been referred to by his name but of which Ollier[14] gave the first published account in 1872.

Instead of using small grafts (2, 3 and 4 mm. in diameter) as Reverdin did, Ollier used grafts 4, 6 and 8 cm. square or even larger, with which he practically covered the denuded area. These grafts proved to be a distinct advance over Reverdin's small grafts, as the method was simple, the grafts were easily and rapidly applied and large areas could be covered in one operation. Time proved, however, that this method had many of the drawbacks of Reverdin's method. The epithelial cover

---

6. Pollock, G. D.: Cases of Skin-Grafting and Skin Transplantation, Tr. Clin. Soc. London **4**:37, 1871.

7. Gillespie: Case of Skin Grafting, Brit. M. J. **2**:603, 1870.

8. Chisolm, J. J.: Skin Grafting, Richmond & Louisville M. J. **10**:353, 1870.

9. Czerny, V.: Ueber die Entstehung der Tuberkulose nach Hauttransplantationen, Centralbl. f. Chir. **13**:18, 1886.

10. Jacenko, A.: Ueber die Transplantation abgetrennter Hautstücke, Med. Jahrb. **3**:416, 1871. Lindenbaum: Ueber die Transplantation Vollständig vom Körper getrennter Hautstücke auf granulirende Flächen, Berl. klin. Wchnschr. **8**:128, 1871.

11. Albanese, E.: Sul trapiantanento dell' epiderme, Gazz. clin. d. sped. civ. di Palermo **3**:206, 1871. Amabile, L.: L'innesto epidermico e la trapiantazione cutanea nella cura della piaghe, Movimento **3**:129, 1871. Marcani, cited by Cotton and Ehrenfried.[3c] Perassi: Rapporto sopra una memoria del Professore Luigi Porta. Sull'innesto epidermico della piaghe, Gior. d. r. Accad. di med. di Torino **37**:538, 1874.

12. Reverdin, J. L.: Sur la greffe épidermique, Arch. gén. de méd. **19**:277, 555 and 703, 1872.

13. Thiersch: Ueber die feineren anatomischen Veränderungen bei Aufheilung von Haut auf Granulationen, Verhandl. d. deutsch. Gesellsch. f. Chir. **3**:69, 1874.

14. Ollier, L.: Greffes cutanées ou autoplastiques. Bull. Acad. de méd. **1**:243, 1872; abstracted, Lyon méd. **9**:464, 1872.

did not prevent contraction; it was not adaptable to wear, slight pressure causing it to ulcerate or slough, and the transplanted skin was prone to undergo discoloration.

The general dissatisfaction led to the revival of the Indian method of full thickness grafting. Wolfe,[15] of Glasgow, Scotland, in 1875 used it successfully in the reconstruction of a lower eyelid. Krause[16] in 1893 described an improved technic which is practically the same as that employed today, and the method is known as the Wolfe-Krause graft.

Some of the drawbacks of the small thin grafts led Davis[17] in 1914 to introduce his small deep grafts; to overcome some of the drawbacks found by experience to accompany the large deep grafts, Blair[18] in 1928 introduced his thick razor, or intermediate split skin, graft. Because of the advantages these two methods have been shown to possess, they have largely replaced the small thin grafts of Reverdin and the large thin razor grafts of Ollier and Thiersch in free skin transplantation.

OTHER METHODS

Many other methods of employing epithelium for grafting have been suggested. Lusk[19] employed the dried cuticle obtained from blisters induced by a vesicating agent, applying it to the denuded area.

Early in the nineteenth century, Dieffenbach[20] reported the successful implantation of hair follicles, but the procedure was later attempted by Wentscher[21] (1898) without success. Scrapings of surface epithelium[22] and shavings of warts, corns and calluses have also been used.[23]

Pollock[6] in 1870 described a method by which he implanted small razor grafts (2 to 4 mm. square) directly into the granulations in much the same way as seeds are planted in the ground. This method was

15. Wolfe, J. R.: A New Method of Performing Plastic Operations, Brit. M. J. **2**:360, 1875.

16. Krause, F.: Ueber die Transplantation grosser ungestielter Hautlappen, Verhandl. d. deutsch. Gesellsch. f. Chir. **22**:46, 1893.

17. Davis, J. S.: The Use of Small Deep Skin Grafts, J. A. M. A. **63**:985 (Sept. 19) 1914.

18. Blair, V. P., and Brown, J. B.: The Use and Uses of Large Split-Skin Grafts of Intermediate Thickness, Surg., Gynec. & Obst. **49**:82, 1929.

19. Lusk, Z. J.: Some Additional Facts Relating to Skin Grafting, J. A. M. A. **29**:782 (Oct. 16) 1897.

20. Dieffenbach, J. F., cited by Cotton and Ehrenfried.[3c]

21. Wentscher, J.: Wie lange und unter welchen Umständen bleibt die Lebensfähigkeit der menschlichen epidermiszellen ausserhalb des Organismus erhalten? Centralbl. f. Chir. **25**:7, 1898.

22. Sée, M.: Greffe épidermique, Gaz. méd., Paris **25**:343, 1870.

23. Hodgen, J. T.: Cell or Skin Grafting, St. Louis M. & S. J. **8**:289, 1871. Leale, C. A.: The Use of Common Warts of the Hand in Skin Grafting, M. Rec. **14**:188, 1878.

revised by Braun [24] in 1920. (Unlike the small deep graft of Davis, this implant does not preserve its identity but fuses imperceptibly with the rest of the skin.)

Westhues [25] described a combined superficial and buried method of skin grafting in which he used long thin strips of skin threaded through a needle, weaving them in and out over the granulating area so that part of the graft remained above and part beneath the surface of the wound.

Von Mangoldt [26] in 1895 revived the method of applying pulpified epithelium to the surface of granulating wounds.

From a practical standpoint none of these procedures has been found sufficiently satisfactory to warrant continued use.

In Pels-Leusden's clinic [1] in Griefswald, Germany, pulpified epidermis was forced into the granulation tissue by means of a small syringe to hasten healing. Reschke [27] made use of this method in treating rodent ulcers. It is this same method which I have found useful in selected cases, and it is one which merits more than random consideration. The result following treatment of an extensive burn of the back and arms of the child in the case reported here cannot be regarded by even the most skeptical as merely accidental.

THE TECHNIC

The area from which the skin for injection is obtained should, if possible, contain skin similar in texture to the skin it is intended to replace. The donor area is prepared the day before the operation by first shaving and then scrubbing thoroughly with soft soap U. S. P. and water, rinsing with sterile water, washing with 70 per cent alcohol and covering with a light aseptic dressing.

Immediately before the operation the area is again thoroughly cleansed with soap and water and then with alcohol followed by ether. The selection of the type of anesthesia will depend principally on the experience of the operator, although I do not believe local infiltration of the donor area to be advisable.

The area from which the skin for transplantation is to be taken is scraped lightly with a sharp knife or a razor, and these scrapings are discarded. The area is then sparingly moistened with physiologic solution of sodium chloride, and small thin sections paralleling the surface

24. Braun, W., cited by Wangensteen, O. H.: The Implantation Method of Skin Grafting, Surg., Gynec. & Obst. **50**:634, 1930.

25. Westhues: Modification der Thiersch'schen Transplantation, Centralbl. f. Chir. **25**:7, 1898.

26. von Mangoldt, F.: Die Ueberhautung von Wundflächen und Wundhölen durch Epithelaussaat; eine neue Methode der Transplantation, Deutsche med. Wchnschr. **21**:798, 1895.

27. Reschke: Epithelisierungsversuche, Arch. f. klin. Chir. **121**:233, 1922.

are removed and placed in an unglazed earthenware mortar. These small sections are further divided by cross cutting with a knife and finally by grinding with a pestle, a small amount of physiologic solution of sodium chloride being added before the grinding is begun.

The area is again scraped, more vigorously than before, and the scrapings are placed in a separate container. As the dermal area is entered, oozing of serum and some bleeding occur, intermingling with the minutely divided skin. Cells, serum and blood are scooped up at intervals and placed in a container until a sufficient quantity is obtained for the immediate need. The tissues collected in the separate containers are then combined, and enough saline solution is added to disperse the

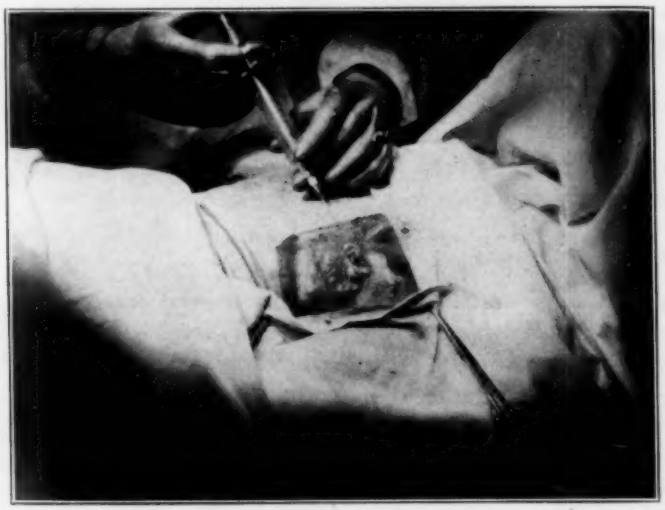


Fig. 1.—Method of injecting the finely divided particles of skin beneath the surface of the granulation tissue.

mixture so that it may be readily drawn into a glass syringe. (To lessen the tendency for the syringe to stick during the injection, the piston and the inside of the syringe barrel may be coated with liquid petrolatum.)

A needle with a bore large enough to allow the mixture to pass readily through is fitted to the syringe, and the contents are injected into the granulation tissue immediately beneath the surface (fig. 1). The needle may be carried for some distance from its point of entrance close beneath the surface, slowly infiltrating the tissue with the dermal suspension as the needle advances or as it is withdrawn. The injections should begin at or close to the margin of the wound and should be repeated at regularly spaced intervals until the entire circumference has

been infiltrated, continuing somewhat nearer the center of the wound with each successive cycle.

Each time the needle is withdrawn some bleeding occurs at the puncture site, but this has never been bothersome, and the blood has been left to coagulate on the surface.

REPORT OF A CASE

D. G., a 9 year old Negress, sustained an extensive burn of her back and arms when, on Nov. 19, 1939, her clothing accidentally caught fire. During the first month treatment with the medicaments commonly used for burns resulted in satisfactory progress, but for the ensuing two and one-half months no further healing was noted.

After this time, three and one-half months after her admission to the hospital, she was seen in consultation because of an increasing contracture deformity of her right arm. Clean, healthy-appearing granulation tissue, somewhat excessive over the lower portion of the back, covered the unhealed area (fig. 2 *A*).

Since prevention of greater contracture and lessening of further deformity of the arm were dependent on a more favorable rate of healing of the cutaneous defect than had taken place in the previous months, it was thought advisable that some method of inducing more rapid healing be adopted. Transplantation of skin by the usual methods and by the method described here were each discussed; the injection method was adopted even though the effects on healing in such a large wound seemed most uncertain.

First Transplantation.—On March 8, 1940, one hundred and ten days after the child's admission to the hospital, the first skin transplantation was made. Ethylene anesthesia was used. Dermal tissue was obtained from an area on the back of the right thigh. Into a band measuring from 3 to 4 cm. at the periphery of the wound on her back and arm the finely divided skin suspended in physiologic solution of sodium chloride was injected (fig. 1). The entire area was then covered with coarse mesh paraffin gauze fixed in place with adhesive tape and a sterile dry dressing. The outer dressings were changed every three to five days as needed, but the coarse mesh paraffin gauze was not disturbed.

During the first ten days there was a decided improvement in the rate of healing. Figure 2 *B* shows the extent of healing on the fifteenth day after the skin transplantation. Since little improvement was noted after the tenth day, it was decided to repeat the transplantation. Therefore, on March 26, on the patient's one hundred and twenty-eighth day in the hospital and eighteen days after the first injection, a second transplantation was made.

Second Transplantation.—The operation was identical with the first; this time the skin used for the injection was taken from the back of the left thigh.

Following this second injection there was a noticeable improvement for the first ten to fifteen days, after which time the rate of further healing noted each time the dressing was changed seemed to be diminishing. Repetition of the injection was at this time purposely postponed until no further improvement could be observed. About the end of the fourth week the healing process seemed to have stopped, and during the succeeding ten days no perceptible improvement occurred. Figure 2 *C* shows the condition of the wound on May 3, thirty-eight days after the second injection and one hundred and sixty-six days after admission.

Fig. 2.—*A*, amount of healing which had taken place during the first one hundred and ten days following the accident. This photograph was taken the day before the first skin transplantation. *B*, amount of healing which occurred during the fifteen days following the first skin transplantation. *C*, extent of healing thirty-eight days after the second skin transplantation. *D*, condition of the wound fourteen days after the third dermal transplant, on the day before the child left the hospital. *E*, wound completely healed October 22, one hundred and fifty days after observation of the condition shown in figure 2 *D*.

Third Transplantation.—On the following day (May 4) another injection was made into the periphery of the wound; the skin used was obtained from the back of the left thigh. Three weeks after this third injection healing had become so nearly complete (fig. 2 *D*) that continued hospitalization seemed unnecessary; the patient was therefore discharged to the outpatient department for subsequent dressings.

The new skin, as it grew in from the margins of the wound, was lacking in pigment for a short period. The width of this unpigmented band of newly formed skin at the periphery varied with the rate of healing, being widest when and where healing was most rapid and narrowing as healing slowed. Pigmentation in the newly formed skin was eventually uniform and noticeably more abundant than in the undamaged skin elsewhere on the child's body, the healed areas being left darker than the surrounding skin. This was particularly true of the patches on the backs of the thighs where skin had been removed for transplantation.

Seventy-eight days elapsed from the time of the first injection (fig. 2 *A*) until the child was discharged from the hospital. At the time of her discharge there was still a small unhealed area on her back (fig. 2 *D*). As she was dependent on an indifferent and wholly unreliable parent to fetch her for surgical dressings, these were changed irregularly and were at times wanting. Healing was not complete (fig. 2 *E*) until October 22. Therefore, it took one hundred and fifty additional days for the small unhealed area present at the time of her discharge from the hospital to become covered with new skin and epithelium. A total of three hundred and thirty-eight days and three skin transplantations by injection were required for the complete healing of the wound.

(Since the completion of healing of the wound on the patient's back and arms, she has been seen at three to six week intervals in order to observe any changes which might occur in the newly formed skin, particularly in the web formation in the right axilla, which partially binds the arm to the chest wall. This axillary web formation will require plastic repair if full motion of the shoulder is to be restored.)

During the first four months following the child's discharge from the hospital the fibrinous tissue was everywhere excessive beneath the surface of the healed area. Across its lower margin on the back and beneath the upper part of the left arm some keloid formation occurred. Except for a narrow band across the middle of the wound, where healing occurred last and was slowest, there was a noticeable lessening in the amount of subcutaneous fibrinous tissue. The new skin elsewhere gradually became pliable enough to be pinched between the fingers, and at the time of writing its texture feels quite like that of the adjacent undamaged skin. Even though it were to be argued that the newly formed skin is not equal in quality to the skin it has replaced, there can be no denying that it is decidedly unlike a mere cicatrix, a criticism commonly made when thin onlay grafts are used.

During the past few weeks there has been a noticeable decrease in the degree of pigmentation in the small area in the middle of the back (fig. 2 *E*) which was the last to heal. It is quite probable that this area may eventually break down or require further surgical attention. The case of this child has thus far been most interesting to observe, and her progress has been comforting to both her attendants and herself.

COMMENT AND SUMMARY

A chronicle of the important contributions to the study and technic of free tissue transplantation is given, and a method for the transplantation of very small particles of skin suspended in saline solution by injecting them beneath the surface of healthy granulation tissue to aid in the healing of an indolent raw surface is again brought to attention.

A striking result recently obtained in an extensive burn of the back and arms of a child is convincing enough to justify presentation of the method for consideration by others.

During the first three or four weeks following the child's accident some improvement was observed from the use of medicaments commonly employed in the treatment of burns, but for the subsequent two and one-half months little if any improvement was noted. One hundred and ten days after the child's admission to the hospital a suspension of finely divided skin was injected into the periphery of the unhealed wound. During the succeeding fifteen days the wound showed more improvement than had occurred in the preceding three and one-half months. Eighteen days after the first injection the procedure was repeated, and again rapid healing was observed for about two weeks. Thereafter, however, healing seemed to diminish with each succeeding change of dressing, so that by the end of the fourth week the healing process had apparently stopped. Thirty-nine days after the second injection the third and last transplantation was done. Three weeks later, when the child was discharged from the hospital, her wound was mostly healed. The lessening of the interim between the second and the third, or last, injection might have further reduced the healing time.

Seventy-eight days elapsed from the time of the first injection until the patient was discharged from the hospital, during which time the major part of the healing occurred.

The small area which was still unhealed when the child was discharged from the hospital took one hundred and fifty days, or seventy-two days more than was required for the healing of the major part of the burn, which took place between the time of the first skin transplant and the day of discharge.

When the amount of healing which took place during the seventy-eight days following the first injection is contrasted with the amount of healing which occurred during the one hundred and ten days preceding the first transplantation and also with the one hundred and fifty days following the child's discharge from the hospital, the difference in the rate of healing during these periods is indeed impressive.

The small area where healing occurred last has in recent weeks shown some retrograde change, evidenced by a lessening in the degree of pigmentation. It is probable that this portion of the healed area,

which is mostly scar tissue, may later break down or require further attention. Except for this small area in the middle of the narrow band traversing the back, which on the right side fuses with the web in the axilla, and also where keloid formation is present elsewhere, the newly formed skin possesses none of the characteristics of mere superficial cicatrix. Indeed, most of it is similar in texture to the adjacent undamaged skin.

Time and extensive trial, with careful attention to the details of its application, will be necessary for proper evaluation of this method of skin transplantation. Its advantages over most of the other methods of free skin transplantation are that it can be used when mild surface infection is present; that it is applicable to wounds widely variable in size as well as in location; that it can be used in parts incapable of immobilization, and that the postoperative dressings need be neither so complicated nor so bothersome.

ACTUAL GROWTH OF YOUNG CARTILAGE TRANSPLANTS IN RABBITS

EXPERIMENTAL STUDIES

S. MILTON DUPERTUIS, M.D.
PITTSBURGH

In the field of plastic and reconstructive surgery the transplantation of cartilage has assumed a role of increasing importance. During the past seventy-five years many reports have appeared in the literature describing the experimental and clinical results of the use of cartilage grafts, but the conclusions presented have often been contradictory. At present the evidence for survival of autografts of cartilage is admitted readily, but similar proof for the viability of isotransplants [1] is not so conclusive. Observations as to whether cartilage grafts were living or dead have depended on the gross and microscopic appearance of apparently viable cartilage cells at the time of removal of the graft. It has been assumed that if a transplant of very young cartilage remains viable in all probability it will resume its regular rate of growth. A demonstrable increase in size of the graft, correlated with the macroscopic and microscopic appearance, would present the clearest evidence for the viability of a transplant and would demonstrate for the first time that young cartilage is capable of continued growth after transplantation. The clinical application of these experiments is limited to the transplantation of cartilage in children. The increasing importance of this measure is discussed later in this paper.

SURVEY OF THE LITERATURE

1. *Experimental Studies on Animal Cartilage Transplantation and Regeneration.*—Interest in the viability and regeneration of cartilage

From the Department of Surgery, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York.

Condensed from a thesis submitted to the faculty of the College of Physicians and Surgeons, Columbia University, in partial fulfilment of the requirements for the degree of Doctor of Medical Science.

1. Throughout the literature with few exceptions there has been an inexact usage of the term homotransplant as defined in American medical dictionaries. To avoid general confusion concerning the exact meaning of the prefix homo- (also homoio- and homeo-), in this report the more precise terms isotransplant and isograft have been employed to connote the transplantation of tissue to or from a subject of the same species.

dates back to an early period. Both Marchand [2] and Lexer,[3] in their comprehensive surveys on the subject of transplantation of tissues, pointed out that Hippocrates, Celsus and Galen either opposed the idea of any regeneration of cartilage or merely admitted that the healing of cartilage wounds was minimal. Concerning the results obtained by the earliest of modern investigators, it is reported that Dorner [4] in 1798 and Meckel [5] and Pauli [6] in 1815, on the basis of experiments on wound healing in various cartilages, concluded that there was no regeneration of cartilage in incised wounds or open defects. In 1851, however, Redfern,[7] employing the microscope for the first time to study the healing of wounds in rib and ear cartilage, described an ingrowth of fibrous tissue into the defect and some cartilage cell activity on the edges of the wound; however, they arrived at no definite conclusions. This brief survey of observations on the healing of cartilage wounds brings one to the period when further studies of the viability and regeneration of cartilage were made with the use of free transplants of tissue.

In 1865, Bert,[8] observing the vascularization of the tail of a rat which had been buried beneath the skin as a free transplant, noticed that the nerve and muscle tissue degenerated early but that the bone tendon and the cartilage remained viable for months. If absorption took place under abnormal conditions, the remnants of the graft were the calcified articular cartilages. Although he did not employ cartilage as a separate graft, this investigator is generally accredited with being the first to report the presence of living cartilage after free transplantation. Free cartilage grafts had been studied previously (in 1852) by Middeldorf,[9] but he reported complete absorption of all grafts.

Ollier [10] (1867) was the first investigator to declare that cartilage requires the presence of its perichondrium for successful transplantation. Working with rabbits and fowl, he found the cartilage transplants

2. Marchand, F.: Der Process der Wundheilung mit Einschluss der Transplantation, in Billroth, T., and Luecke, A.: Deutsche Chirurgie, Stuttgart, Ferdinand Enke, 1901, no. 16.

3. Rehn, E., and Ruef, H.: Die freie Knorpeltransplantation, in Lexer, E.: Die freie Transplantationen, in von Bruns, P.: Neue deutsche Chirurgie, Stuttgart, Ferdinand Enke, 1924, vol. 2, pp. 286-369.

4. Dorner, cited by Rehn and Ruef.[3]

5. Meckel, cited by Rehn and Ruef.[3]

6. Pauli, cited by Marchand.[2]

7. Redfern, cited by Lefas [20] and Rehn and Ruef.[3]

8. Bert, P.: Sur la greffe animale, Compt. rend. Acad. d. sc. **61**:587, 1865.

9. Middeldorf, cited by Rehn and Ruef.[3]

10. Ollier, L.: Traité expérimental et clinique de la regénération des os et de la production artificielle du tissu osseux, Paris, V. Masson & fils, 1867, vol. 1, p. 162.

viable after 3 months. Wounds in the articular cartilage of young rabbits healed, but similar wounds in adult rabbits showed no repair. Many of the smaller cartilage grafts in dogs and in fowl were absorbed, however. Likewise, in 1878 Tizzoni [11] described fatty degeneration occurring in cartilage cells after a few days of implantation and the disappearance of the grafts in the granulation tissue which enveloped them.

Zahn [12] in 1877 reported similar failures with small pieces of adult rib cartilage grafts, regardless of the locality to which the grafts were transplanted. In later trials with fetal cartilage, however, he observed definite growth, with activity limited to the cells on the periphery; the greatest increase in size occurred where the blood supply was best. Leopold [13] in 1881 demonstrated a luxuriant development of fetal cartilage transplants placed in the abdomen, in the jugular vein or in the anterior chamber of the eye. In some instances fetal grafts increased in size over three hundred fold during a period of 200 days. Because he was unable to observe any growth in transplants of non-fetal cartilage in rabbits, he concluded that ordinary cartilage grafts remained stationary, shrank or eventually were absorbed, whereas fetal cartilage grafts always grew, even as heterotransplants. In the same year (1881), one other investigator, Gies,[14] reported no healing of cartilage defects on joint surfaces in clean wounds after 150 days.

Prudden [15] (1881), in a carefully controlled series of experiments, supplied further proof that living cartilage can be transplanted successfully. He placed 200 small fragments of hyaline cartilage from the head of the femur and the chondral section of the ribs of a freshly killed rabbit into the subcutaneous tissues of a living rabbit, and evaluated his results by studying over 1,200 microscopic slides of sections removed at intervals varying up to 399 days. Among other conclusions, he emphasized that transplanted cartilage may live for many months and that cells may change their shape and size, entering into the formation of embryonal cartilage or taking an active part in the formation of new connective tissue. Because these bits of cartilage were taken with the greatest care to exclude any perichondrium, it was indicated for the first time that cartilage transplants may survive without attached perichondrium.

---

11. Tizzoni, G.: Sulla istologia normale e patologica delle cartilagini ialine, Arch. per le sc. med. **2**:27, 1877-1878.

12. Zahn, F. W.: Sur le sort des tissus implantés dans l'organisme, Congr. méd. internat. de Génève, 1877, p. 658.

13. Leopold, G.: Experimentelle Untersuchungen über die Aetiologie der Geschwülste, Virchows Arch. f. path. Anat. **85**:283, 1881.

14. Gies, T.: Ueber Heilung von Knorpelwunden, Arch. f. klin. Chir. **26**: 848, 1881.

15. Prudden, T. M.: Experimental Studies on the Transplantation of Cartilage, Am. J. M. Sc. **82**:360, 1881.

Diametrically opposed to this observation were the results of Fischer's [16] work on costal cartilage (1882), which led him to support Ollier's [10] original contention that transplants without perichondrium would not survive. After showing transitory cellular growth, cartilage grafts without perichondrium always degenerated in about 8 weeks, he found, but costal cartilage with its perichondrium intact showed no alteration in structure. One of his most valuable contributions was the observation that the younger the cartilage transplant the greater is its power of regeneration and its innate viability. Likewise, his research on fetal cartilage transplants substantiated the findings of previous investigators (Zahn;[12] Leopold [13]) in the demonstration of tremendous growth possibilities of this tissue.

By this time it was fairly well established that with a favorable environment and the use of a careful technic cartilage transplants will survive. Later investigations have verified Prudden's [15] original observation that grafts of cartilage denuded of their perichondrial coverings will remain viable. At this point it becomes increasingly difficult to untangle the maze of contradictory results; so an effort is made to relate only the general trend of modern investigation on this subject by giving a few details of the more important contributions.

Von Mangoldt [17] in 1899 gave both experimental and clinical evidence that transplanted cartilage survived for periods up to 19 months. Von Helferich [18] (1899) claimed rather poor results from his work with epiphysial cartilage transplants in rabbits, while Enderlen [19] reported in the same year that reimplanted epiphysial cartilage displayed remarkable viability. Lefas [20] in 1902 affirmed that no real repair was evident in articular cartilage wounds, while Pennisi,[21] two years later, demonstrated definite areas of cartilaginous proliferation beyond the area of necrotic cells along the edge of the wound. On the basis of contributions by Marchand [2] verifying the findings of Pennisi [21] and others, it appears that some regenerative power in cartilage is being recognized, and these investigations emphasize not only the transplantability of cartilage but the possibility of actual growth.

---

16. Fischer, E.: Ueber Transplantationen von organischen Materiel, Deutsche Ztschr. f. Chir. **17**:362, 1882.

17. von Mangoldt, F.: Ueber die Einpflanzung von Rippenknorpel in den Kehlkopf zur Heilung schwerer Stenosen und Defecte, Verhandl. d. deutsch. Gesellsch. f. Chir., 1899, p. 613.

18. von Helferich: Versuche über die Transplantation des Intermediärsknorpels wachsender Röhrenknochen, Deutsche Ztschr. f. Chir. **51**:564, 1899.

19. Enderlen: Zur Reimplantation des resecirten Intermediärknorpels beim Kaninchen, Deutsche Ztschr. f. Chir. **51**:574, 1899.

20. Lefas, E.: Sur la réparation du cartilage articulaire, Arch. de méd. expér. et d'anat. path. **14**:378, 1902.

21. Pennisi, A.: Sul processo di guarigione delle ferite delle cartilagini, Policlinico (sez. chir.) **11**:489, 1904.

Seggel [22] in 1904 found degeneration in most of his adult cartilage grafts, while Judet [23] pointed out that transplants survive best in young animals. As the result of his experiments, Axhausen [24] in 1912 concluded that the transplantation of joint cartilage as an isograft has the greatest practical application.

Davis [25] (1913) placed large pieces of rib cartilage in pedunculated flaps on dogs, and the cartilage remained viable with no evidence of absorption or degeneration either macroscopically or microscopically. The grafts shrank little, if at all, during a period of 4 months; apparently they were receiving nourishment and were not being tolerated merely as foreign bodies. Four years later the same author, working on free grafts of cartilage and bone,[26] showed that cartilage lived for 582 days, while bone was almost completely absorbed. There were no evidences of absorption in the cartilage grafts, although the sharp edges had become smooth, and the microscopic picture showed normal living cartilage of good staining quality with some central calcification and slight absorption. Davis asserted clearly that the presence or absence of the perichondrium seemed to have little effect on the nourishment of the cartilage cells.

Nageotte [27] in 1917 described proliferation of new cartilage cells along the edges of wounds in living cartilage, and Nussbaum [28] in the following year found that free transplants of cartilage might show absorption of the older cartilage cells by an ingrowth of young cells from the perichondrium without the aid of lymphocytes or blood vessels. In correlating his own experimental observations with an extensive survey of the existing literature, Lexer [3] (1925) concluded that hyaline cartilage (rib and joint) has a marked ability to survive as a living transplant.

More recently, Mannheim and Zypkin [29] studied autogenous cartilage grafts in rabbits for a year and similar transplants in dogs for 30

22. Seggel, R.: Verhalten des Knorpels bei Uebertragung in die freie Bauchhöhle, Deutsche Ztschr. f. Chir. **75**:326, 1904.

23. Judet, cited by Rehn and Ruef.[3]

24. Axhausen, G.: Ueber den histologischen Vorgang bei der Transplantation von gelenkenden, insbesondere über die Transplantationsfähigkeit von Gelenkknorpel und Epiphysenknorpel, Arch. f. klin. Chir. **99**:1, 1912.

25. Davis, J. S.: Transplantation of Rib Cartilage into Pedunculated Skin Flaps: An Experimental Study, Bull. Johns Hopkins Hosp. **24**:116, 1913.

26. Davis, J. S.: A Comparison of the Performance of Free Transplants of Bone and Cartilage: An Experimental Study, Ann. Surg. **65**:170, 1917.

27. Nageotte, J.: L'organisation de la matière dans ses rapports avec la vie, Paris, Félix Alcan, 1922, p. 96.

28. Nussbaum: Ueber Epithel- und Knorpeltransplantation bei Trachealdefekten, Beitr. z. klin. Chir. **110**:101, 1918.

29. Mannheim, A., and Zypkin, B.: Ueber freie autoplastiche Knorpeltransplantation, Arch. f. klin. Chir. **141**:668, 1926; abstracted, J. A. M. A. **87**:2132 (Dec. 18) 1926.

months.[30] They concluded that (*a*) grafts placed in the subcutaneous tissues showed a reduction in thickness of the perichondrium with some evident cellular destruction and replacement by fibrous tissue; (*b*) the cartilage transplants buried in muscle were in the finest state of preservation, while those placed in the skull were inferior to grafts in the subcutaneous tissues, and (*c*) partial removal of the perichondrium *increased* the viability of a cartilage graft—a completely new idea.

Loeb[31] in 1926 and 1927 added further knowledge to the subject of cartilage transplantation by presenting a most interesting series of investigations, which was supplemented in 1935 by an article by Loeb and Siebert.[32] In the guinea pig, autografts of cartilage were usually preserved *in toto,* with an occasional minor tissue reaction observed after periods varying up to 5½ months. Isografts always provoked a distinct lymphocytic reaction, a marked increase in connective tissue and increased destruction of the cartilage by invading lymphocytes and fibrocytes. In another experiment on rats Loeb established a definite correlation between the genetic relation of the donor with the host and the severity of tissue reaction on the part of the host against implants. Thus, in "syngenesiotransplantation" there was less reaction on the part of the host tissues to grafts of close familial and genetic origin. As conclusive proof that transplanted cartilage can survive for long periods, serial transplantation of a piece of cartilage was carried on in rats for over 6 years, which is twice the normal life span. Loeb concluded that cartilage, in comparison with other tissues, exhibits greater viability in transplantation because of (*a*) a diminution in the homoiotoxic, or isotoxic, reaction on the part of the host tissues toward cartilage; (*b*) a greater resistance of cartilage (because of its hyaline substance) toward the instruments of attack (lymphocytes and connective tissue cells), and (*c*) the lower tissue metabolism of cartilage, which favors survival until nourishment is established for the graft.

In a more recent paper, Borst[33] (1928) maintained that the regeneration of cartilage depends on the perichondrium, although denuded cartilage can remain alive after transplantation. Gorbunoff[34] found

30. Mannheim, A., and Zypkin, B.: Späteresultate der Knorpelplastik, Arch. f. klin. Chir. **149**:31, 1927.

31. Loeb, L.: Autotransplantation and Homoiotransplantation of Cartilage in the Guinea Pig, Am. J. Path. **2**:111, 1926; Autotransplantation and Homoiotransplantation of Cartilage and Bone in the Rat, ibid. **2**:315, 1926; Transplantation and Potential Immortality of Mammalian Tissues, J. Gen. Physiol. **8**:417, 1926; Syngenesiotransplantation in the Rat, Am. J. Path. **3**:45, 1927.

32. Loeb, L., and Siebert, W. J.: Transplantation of Skin and Cartilage in Chickens, Arch. Path. **20**:28 (July) 1935.

33. Borst, M.: Das pathologische Wachstum, in Aschoff, L.: Pathologische Anatomie, ed. 1, Jena, Gustav Fischer, 1928, p. 611.

34. Gorbunoff, W. P.: Vergleichende Studien über die Knochen- und Knorpel-Auto- und Homotransplantation, Arch. f. klin. Chir. **161**:651, 1930.

that his isografts resisted absorption nearly as well as autotransplants. Finally, Fohl [35] (1929) and Pereira and Dupertuis [36] (1936) determined that fresh autografts of epiphysial cartilage survived, even to the extent of producing typical bony exostoses.[36]

Therefore, on the basis of this survey one may conclude: (*a*) that fresh animal cartilage with or without its perichondrium will survive as a viable autotransplant or isotransplant for many months; (*b*) that isografts cause a greater cellular response on the part of the host tissues and exhibit more evidence of destruction and invasion by fibrous tissue; (*c*) that under favorable circumstances cartilage demonstrates some regenerative power, which is closely associated with the presence of its perichondrium, and (*d*) that young cartilage retains its viability better than does adult tissue and survives best in host tissues with the greatest vascularity.

2. *Heterotransplantation.*—Almost universally, investigators agree that the heterotransplantation of tissues is doomed to failure. On this subject, Lexer [3] emphasized that a heterograft of joint or rib cartilage with or without its perichondrium absorbs completely in a few months. In 1916, Imbert [37] and his co-workers used young beef cartilage from the scapula to fill in cranial defects and found that connective tissue adhesions permitted its temporary survival. He made the observation that the progressive attack and absorption are a biologic process since the heterograft was not ejected as a dead sequestrum. Likewise, Loeb [38] demonstrated that the injurious body fluid action of the host is strongest against heterografts and that even dead heterogenous tissue may evoke this marked tissue reaction.

3. *Use of Dead or Preserved Cartilage for Grafts.*—Recently there has been a revival of interest in the clinical possibilities of preserved cartilage ultimately replacing autogenous grafts. The first animal experiments were carried out fifty-nine years ago, by Prudden,[15] who reported complete absorption of all grafts after fixation by 95 per cent alcohol, phenol, electric desiccation, burning, boiling or drying. Seggel [22] in 1904 noted early destruction of his alcohol-preserved grafts, but Regoli [39] (1922) decided that preserved tissue might prove useful

35. Fohl, T.: Weitere Versuche über die Transplantation der Knorpelfuge, Arch. f. klin. Chir. **155**:232, 1929.

36. Pereira, S., and Dupertuis, S. M.: Recherches expérimentales sur la pathogénie des exostoses ostéogéniques à l'aide de greffes de cartilage de conjugaison, Presse méd. **44**:162 (Jan. 25) 1936.

37. Imbert, L.; L'Heureux, C., and Rouslacroix: Recherches sur les greffes cartilagineux hétéroplastiques, Rev. de chir. **52**:111, 1916.

38. Loeb, L., and Harter, J. S.: Heterotransplantation of Cartilage and Fat Tissue and the Reaction Against Heterotransplants in General, Am. J. Path. **2**:521, 1926.

39. Regoli, G.: Innesti di tessuti morti fissati e conservati, Policlinico (sez. chir.) **29**:559, 1922.

because "neocartilage" appeared as a substitute for the dead cartilage, which in itself never became revivified. Nageotte,[40] on the other hand, discovered that alcohol-preserved cartilage grafts were rapidly fragmented by the invasion of connective tissue cells and appeared to exert a specific action favoring the transformation of connective tissue into bone rather than new cartilage cells. Employing similar methods of fixation, Polettini [41] (1923), Nigrisoli [42] (1927) and Didier and Guyon [43] (1928) described invasion and absorption of these grafts with occasional formation of "neocartilage" or bone.

Considering the clinical possibilities of preserved cartilage, Gorbunoff [34] noted experimentally that his fresh cartilage autotransplants showed a greater decrease in size through absorption than did the preserved grafts during the same period. On the basis of this observation and of the recognized ability of preserved cartilage to be replaced by firm, living connective tissue, this author predicted that preserved transplants probably will replace autoplastic and alloplastic materials. A clinical report on the use of cartilage preserved in physiologic solution of sodium chloride and merthiolate (4:1) appeared in 1938 (O'Connor and Pierce [44]). These workers found that preserved cartilage isografts at times provoked slightly more local tissue reaction than did fresh autografts but showed less tendency to bend and curl. After five years in this series of 375 grafts no absorption had occurred; the grafts had shown a conspicuous ability to resist infection, and in each case (except 6 cases of infection) the transplants had retained their original size and identity. More recently Peer [45] has reported the progressive invasion and partial absorption of alcohol-preserved human rib and septal cartilage grafts after periods varying up to 2 years. He observed no destruction or invasion by fibrous tissue in fresh autografts up to 6 years and therefore concluded: "Autogenous rib cartilage is better material for plastic repair than dead, pickled cartilage." Finally,

40. Nageotte, J.: Escarre par dessication du cartilage auriculaire vivant et des portions dénudées de greffes cartilagineuses mortes; mode d'élimination et phenomènes consécutifs, Compt. rend. Soc. de biol. **80**:689, 1917.

41. Polettini, B.: Su neoformazioni cartilaginee ed ossee determinate da innesti di frammenti di cartilagine e d'osso fissati, Arch. ital. di chir. **6**:179, 1922; abstracted, J. A. M. A. **80**:360 (Feb. 3) 1923.

42. Nigrisoli, P.: Experimenti di innesto di cartilagine fissata nel rene e di sostituzione di parti scheletriche con cartilagine fissata, Arch. per le sc. med. **49**:689, 1927.

43. Didier, R., and Guyon, L.: Production de cartilage et d'os, au sein de greffes vivantes et mortes, chez le lapin, Compt. rend. Soc. de biol. **98**:443, 1928.

44. O'Connor, G. B., and Pierce, G. W.: Refrigerated Cartilage Isografts, Surg., Gynec. & Obst. **67**:796, 1938.

45. Peer, L. A.: (*a*) Experiments on Alcohol Preserved Cartilage in Humans, Arch. Otolaryng. **27**:42 (Jan.) 1938; (*b*) Fate of Living and Dead Cartilage Transplanted in Humans, Surg., Gynec. & Obst. **68**:603, 1939.

Brown [46] in 1940 presented his experiences in the clinical use of preserved cartilage and expressed the opinion that it should be regarded as a second choice substitution when a fresh autograft or isograft is not advisable.

It appears from this experimental evidence that preserved cartilage grafts undergo absorption and may be replaced eventually by fibrous tissue. Clinical reports have been more encouraging, and in many cases these grafts may prove satisfactory, but when permanent support is desired it is dubious whether preserved grafts will replace fresh autotransplants.

4. *Actual Growth of Cartilage Transplants.*—A search through the literature has failed to reveal any experimental data relating to a measurable increase in size occurring in a living graft of young permanent cartilage. Earlier investigators have reported that young cartilage has a greater viability than adult tissue, but the possibility of true growth after transplantation has not been advanced. For the most part statements regarding growth have been negative, and frequently there has been an inexact use of this term to denote survival or viability of the graft. The only experimental background for these studies on the actual growth of young cartilage transplants, therefore, consists of sporadic statements throughout the literature.

One of the most interesting observations on this subject was offered by Bert [8] in his original paper in 1865. He discovered that the denuded tail of a rat when implanted beneath the skin as a free graft kept pace with the rest of the animal in the matter of growth but never grew larger than normal. Two years later, Ollier [10] grafted different types of cartilage in very young dogs; rapid absorption (but never any growth) occurred in all transplants. It is to be noted that Zahn,[12] Leopold,[13] Fischer [16] and von Helferich [18] reported vigorous growth of fetal cartilage under varying conditions of implantation but never any evidence of growth in nonembryonal cartilage transplants. In 1924, Lexer,[3] in his comprehensive survey of a great number of experiments on cartilage transplantation, established that no increase in volume from expansion or swelling occurred; any changes in such grafts were regressive rather than progressive. Various authors [47] have reported actual growth in epiphysial cartilage transplants, often with the ultimate formation of bone, but grafts of temporary cartilage hardly enter the scope of this study. Finally, in the modern literature, Davis,[25] Didier and Guyon [43] and Peer [45b] did not observe any increase in the size of their grafts.

46. Brown, J. B.: Preserved and Fresh Homotransplants of Cartilage, Surg., Gynec. & Obst. **70**:1079, 1940.

47. Seggl.[22] Fohl.[35] Pereira and Dupertuis.[36]

The paucity of experimental observations on the possible growth of cartilage after transplantation is probably the result of two factors: (*a*) the fact that the large majority of investigators employed adult cartilage and (*b*) the fact that this phase of cartilage transplantation has a more limited clinical and practical application.

EXPERIMENTAL STUDIES ON THE GROWTH OF YOUNG CARTILAGE TRANSPLANTS

Plan, Material and Method.—The object of this investigation was to study the growth of young permanent cartilage when transplanted under various conditions. The rabbit appeared to be the animal best suited for this purpose, because

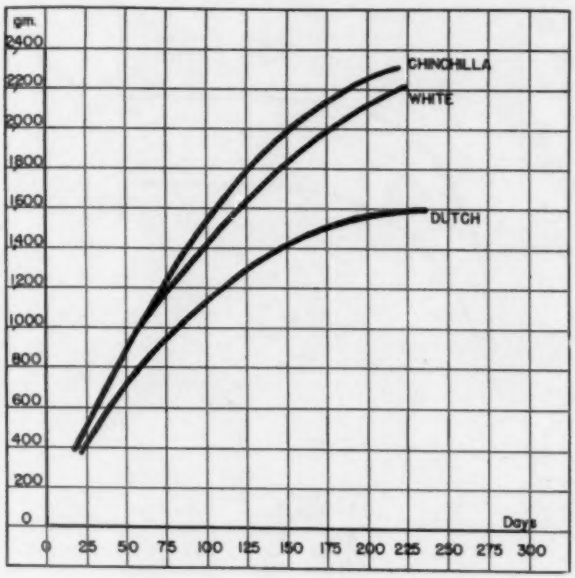


Fig. 1.—Normal weight curves.

the ear affords a generous supply of material and in the very young is still of sufficient size to allow grafts of measurable area to be obtained. The rabbit ear enlarges rapidly in the first few months of life, and the rate of growth is greater than the corresponding increase in weight (figs. 1 and 2). With ordinary precautions infection seldom occurred, and the baby rabbits tolerated the operative procedures exceedingly well.

Three different strains of rabbits were used in these experiments. The chinchilla, or gray, variety and the pure white strain are larger and show grossly a greater increase in the size of the ear during growth (fig. 2). The Dutch, or black and white, breed tolerates all experimental procedures well but is smaller and shows less growth over a given period. These different breeds were employed simultaneously in some of the trials with isografts to eliminate the factor of close genetic relationship.

In all, 107 separate cartilage grafts were observed for periods varying up to 253 days. In order to obtain comparable conditions for growth, several transplants were placed in the same animal. Twenty-six rabbits between the ages of 12 and 24 days were selected; 2 died immediately after operation as the result of an overdose of the anesthetic. Several died after two or three months from intercurrent disease, but their grafts were included in the final results. Feeding problems were of minor importance, because the mother accepted the young rabbits back into the litter, and in every case they nursed well.

A careful record was kept of the weight of each animal before operation and at the time of examination of the specimen. Only one ear was used as a donor site for cartilage, which permitted measurements of length on the alternate side to be utilized as an accurate control. Many of the grafts were held in place

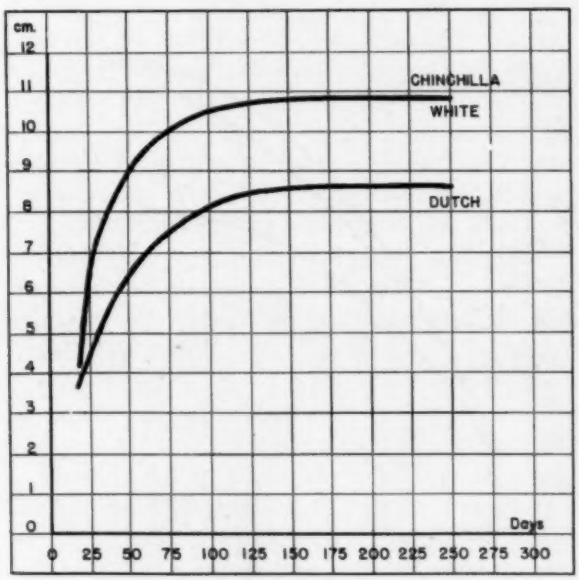


Fig. 2.—Growth curves of control ears.

with fine silk sutures, which also served as markers. This did not introduce a variable factor, for the microscopic sections showed only the slightest localized foreign body reaction, with an occasional giant cell.

Technic.—Each transplantation was performed with the utmost surgical precision. Preparation of the skin consisted of shaving, cleansing with soap and water and application of tincture of iodine. Excess iodine was sponged off carefully with alcohol, and each area was draped with sterile towels. Mosquito hemostats, fine forceps, small curved scissors and regulation eye needles allowed a careful, gentle technic to be employed. Each wound was closed, in layers when necessary, by interrupted sutures of B-Deknatel braided silk. Careful hemostasis and accurate approximation of the edges of the skin were carried out, so no dressings were necessary. On the seventh day the remaining skin sutures were removed, and in the entire series only 2 grafts were extruded from infected wounds. The transplants were kept in a sponge moistened with saline solution

while closure of the donor site and preparation of the recipient bed were carried out. The time required for this averaged fifteen to thirty minutes for the autografts and up to forty-five minutes for the isografts.

When this problem was planned, the question of anesthesia for these very young rabbits presented some difficulties. The margin of safety with ether or with any of the various intraperitoneal drugs was considered too small to permit their use. Local infiltration with procaine hydrochloride solution proved to be the practical answer to this problem. Clinically, local anesthesia has had no delecterious effects on transplants; as it was used successfully in each experiment, no variable factor was introduced. The rabbits submitted to the injection without struggle or manifest pain and lay quietly, tied in place, for operations lasting an hour or

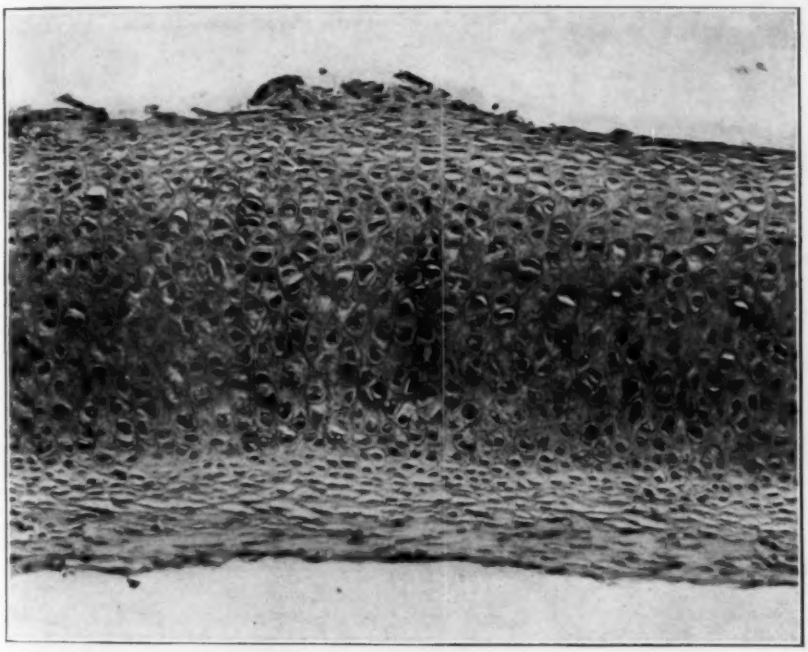


Fig. 3.—Cross section of normal ear cartilage in a 21 day old rabbit. Compare with figure 4.

more. Two rabbits died within forty-eight hours of operation, seemingly from the toxic effects of about 5 cc. of 1 per cent procaine hydrochloride. A solution of 0.5 per cent with 10 drops of epinephrine hydrochloride solution (1:1,000) added to each ounce (30 cc.), for hemostatic purposes, proved safe when injected in quantities of 2 to 3 cc.

The microscopic sections were fixed in Bouin's solution and stained with hematoxylin and eosin. Acid orcein stain was used to identify elastic fibrils in ear cartilage, and the trichrome method was employed to differentiate connective tissue in selected sections.

Series 1: Autotransplants of Ear Cartilage in Young Rabbits.—Procedure: In rabbits 14 to 21 days old (average age, 17.6 days), 9 separate measured pieces

TABLE 1.—*Results in First Series*

Position of Graft	Number and Breed of Rabbit	Age at Operation, Days	Duration of Experiment, Days	Weight, Gm.		Ear Length, Cm.		Per Cent Increase in Ear Length	Size of Graft, Cm.		Per Cent Increase in Length of Graft	Per Cent Increase in Area of Graft
				Operation	Autopsy	Operation	Autopsy		Operation	Autopsy		
Subcutaneous.....	301 (Chinchilla)	17	85	325	1,300	5.0	11.5	130	0.6 × 0.35	1.5 × 0.9	150	542
Muscle.....	301 (Chinchilla)	17	85	326	1,300	5.0	11.5	130	0.7 × 0.3	1.8 × 0.9	157	671
Subcutaneous.....	302 (Chinchilla)	17	71	180	855	4.2	10.0	138	0.6 × 0.5	1.3 × 0.7	117	203
Muscle.....	302 (Chinchilla)	17	71	180	855	4.2	10.0	138	0.6 × 0.5	1.5 × 1.0	150	400
Ear.....	317 (Dutch)	14	253	225	1,500	3.5	9.1	160	0.6 × 0.4	1.3 × 0.9	117	388
Ear.....	318 (White)	18	253	285	2,160	4.8	10.8	127	0.6 × 0.5	1.7 × 1.4	183	692
Subcutaneous.....	311 (Chinchilla)	20	22	395	880	5.9	9.2	56	5.7 × 1.5	6.0 × 1.75	5	27
Subcutaneous.....	311 (Chinchilla)	20	22	395	880	5.9	9.2	56	4.5 × 1.7	5.9 × 2.6	31	100
Subcutaneous.....	312 (Chinchilla)	20	137	385	1,905	5.8	10.0	73	3.8 × 1.4	5.0 × 2.5	33	135
Subcutaneous.....	298 (Chinchilla)	16	223	230	2,235	4.1	11.0	168	2.3 × 2.0	6.5 × 3.7	183	422
Subcutaneous.....	300 (Chinchilla)	16	128	230	.....	4.0	10.0	150	2.2 × 1.7	5.3 × 4.5	141	537
Subcutaneous.....	305 (Chinchilla)	21	222	185	2,350	4.2	11.0	162	0.8 × 0.5	2.1 × 1.5	163	688
Muscle.....	305 (Chinchilla)	21	222	185	2,350	4.2	11.0	162	0.85 × 0.4	2.6 × 1.4	206	1,070
Subcutaneous.....	306 (Chinchilla)	21	39	240	.....	4.3	9.7	125	1.4 × 0.8	2.3 × 1.1	65	124
Muscle.....	306 (Chinchilla)	21	39	240	.....	4.3	9.7	125	1.0 × 0.45	1.8 × 0.9	80	259
Ear.....	317 (Dutch)	14	253	225	1,500	3.5	9.1	160	0.4 × 0.25	1.1 × 0.6	175	560
Ear.....	318 (White)	18	253	285	2,160	4.8	10.8	127	0.65 × 0.5	1.4 × 0.7	116	174
General average.....	17 grafts	18	140	...	.....	...	....	128	.....	.....	122	413
Ear, average.....	4 grafts	16	253	...	.....	...	....	144	.....	.....	147	453
Muscle, average.....	4 grafts	19	104	...	.....	...	....	139	.....	.....	148	600
Subcutaneous, average...	4 grafts	19	104	...	.....	...	....	139	.....	.....	124	389

of fresh ear cartilage were implanted into subcutaneous pockets on the back of the same animal. Prompt healing of the wounds followed in each case, and the grafts were examined at varying intervals up to 253 days. As a general rule these grafts remained flat under the skin and could be palpated and seen rather easily. In 4 animals of this group similar grafts were buried in the posterior muscles of the thigh for a comparison of the development of the transplant in a more vascular bed. In 4 other rabbits small portions of ear cartilage were removed, measured and sutured back into place; these were to demonstrate the reaction of free grafts when returned to their own environment.

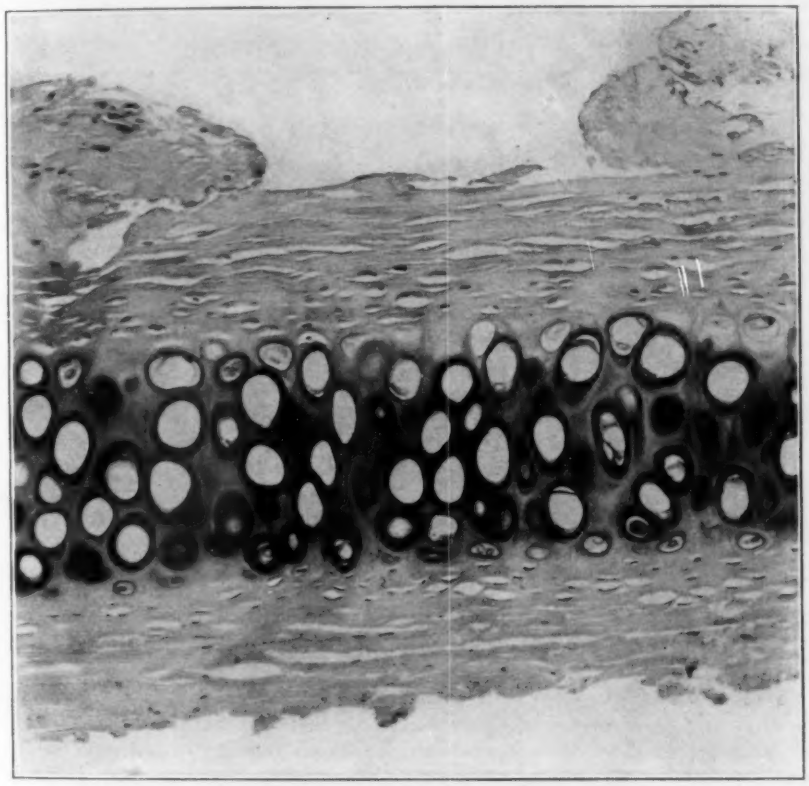


Fig. 4.—Cross section of normal ear cartilage in an adult rabbit. For comparison, the photomicrograph of young cartilage in figure 3 is of the same magnification.

Results: During an average growth period of 140 days, each of the aforementioned 17 autotransplants from rabbits 2 to 3 weeks old exhibited a measurable increase in size. During the same period the control ear increased its length by 128 per cent, while an average of the measured length of the grafts at the time of examination showed an increase of 122 per cent. (The transplants were taken with the longer side always in the long axis of the ear.) The average increase in surface area was 413 per cent, whereas roughly the increase in surface

area of the control ear (calculated by taking the square of the increase in ear length) was 419 per cent.

In the 4 animals in which similar grafts were buried beneath the skin and in the thigh muscles of the same rabbit for comparison, a considerably greater increase in size was found in each of the latter group. During an average period of 104 days for these 4 animals the subcutaneous grafts averaged an increase in length of 124 per cent, as compared with 148 per cent for those implanted in muscle; as for the average increase in area, the ratio was 389 per cent to 600 per cent for the muscle group.

When the cartilage graft was replaced in its donor site in the ear, the average increase in length of 147 per cent indicated additional growth over the general average. As for area, the result of 453 per cent gain is close to the

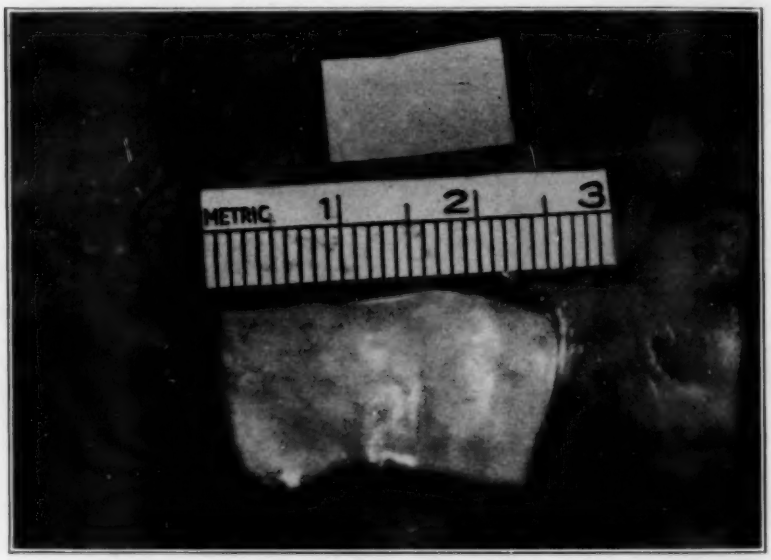


Fig. 5 (rabbit 306, series 1).—Photograph of an autotransplant of young ear cartilage still adherent to the under surface of the skin of the back. The piece of paper immediately above the metric scale shows the size of the graft before transplantation. There were 65 per cent increase in length and 124 per cent increase in area during a period of 39 days.

general average but well below the muscle group, even though these grafts were undisturbed for a much longer period (253 days).

Microscopic Observations: All transplants gave microscopic confirmation of the presence of living, growing cartilage. The intercellular substance stained well with the basophilic dye, and the cells appeared viable. In the older specimens the cartilage became less cellular, approaching typical adult cartilage in appearance, and the perichondrium was thinner and less active, but intact. In all the slides fibrous tissue could be seen about the grafts, but there was no suggestion of active penetration by it. The amount of connective tissue present was variable but not excessive, and about an occasional silk suture was found a small localized reaction with a few giant cells.

Each of the grafts gave indication of growth by apposition at the ends. Here the perichondrium had developed around the free edge, and younger transitional cartilage cells surrounded by paler-staining matrix were in evidence (fig. 6). Only one localized area of degeneration could be distinguished in this series, and no calcification, absorption or bone formation was present.

In only one of the implants into muscle was there microscopic evidence of increased growth activity on the free edge. In another of this group a blood vessel was identified in the perichondrium (fig. 7). Of the 4 animals in which the grafts were replaced in the ear, all had fibrous bridging of the defect between

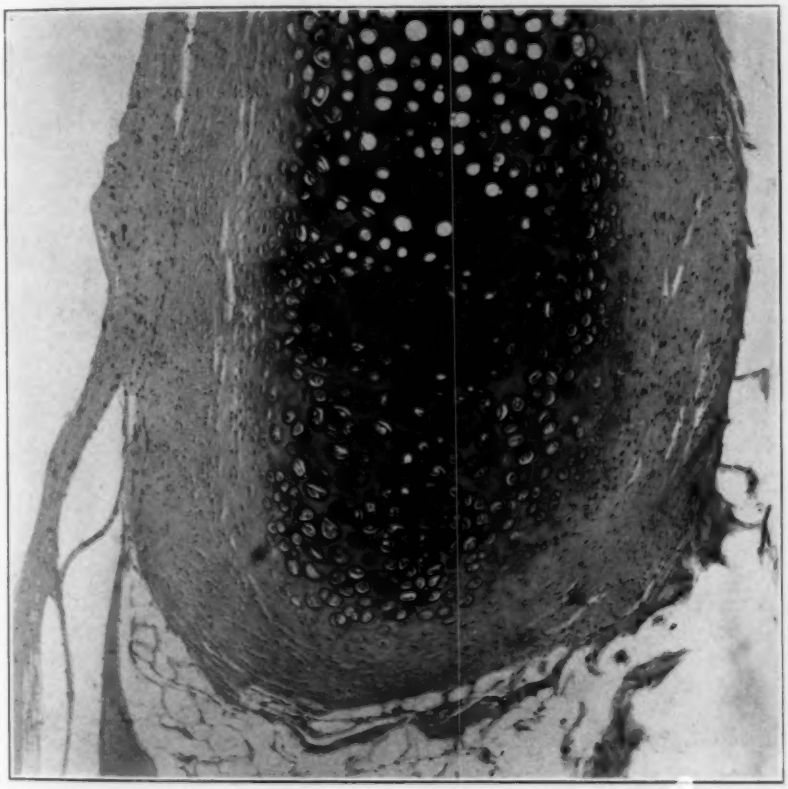


Fig. 6 (rabbit 300, series 1).—Photomicrographic cross section of one edge of a young ear cartilage autograft which had been placed beneath the skin for 128 days. The proliferation of young cartilage cells is apparent about the lower portion of the cartilaginous plate. (Compare with figure 10.)

the implant and the adjacent normal ear cartilage; often proliferative activity was apparent about these areas, but no complete bridge of cartilage tissue was present. Elastic fibrils in the matrix substance were difficult to identify in the routine sections but could be recognized easily when special staining methods were used.

In the original plan of experiment observation of the role of the perichondrium in growth was included. Actually this proved impractical, because the control

sections of ear cartilage from which the perichondrium presumably had been denuded still showed portions attached to the graft. The cartilage plate in these young rabbits was so thin and fragile that more vigorous efforts to remove the perichondrium were futile. Macroscopically one of the implants returned to the original site in the ear showed less growth than the control ear. In this case the normal ear cartilage adjacent to the implant had wrinkled; seemingly it was retarded in its normal development by fibrous adhesions to the graft.

Fig. 7 (rabbit 302, series 1).—Blood vessels located in the perichondrium and partially surrounded by young proliferating cartilage cells. A few strands of striated muscle can be seen in the lower right hand corner.

Series 2: Isotransplants of Ear Cartilage in Young Rabbits.—Procedure: In this series the age of the young rabbits at the time of transplantation was 12 to 24 days (average, 20 days). By a method comparable to that used in the preceding group, 6 separate measured pieces of ear cartilage were inserted into the subcutaneous tissues of the back in litter mates. In another group, 6 implants were put beneath the skin of the back in rabbits of different breed. Likewise, 2 further portions of ear cartilage of equal size from rabbits not genetically related were exchanged and sutured into the aural defects. One infection occurred in this series.

Results: At the end of the average period of growth for this series, 173 days, each individual transplant demonstrated unmistakable gross increase in size. The control ears during this same period averaged 107 per cent increase in length, while the grafts showed but 56 per cent greater length. The surface area of these transplants indicated 155 per cent of growth, as compared with 328 per cent (calculated) for their controls. From these data it is obvious that the isografts did not grow so vigorously as did the autogenous transplants in the preceding series.

The comparison of the 6 isotransplants in litter mates with the group of 6 pieces inserted into similar areas on rabbits of a different breed provided an average increase of length by 52 per cent in 135 days for the litter mates and 61 per cent during a period of 198 days for the latter group. In averaging the growth in surface area, the result was 172 per cent, as compared with 156 per cent for

Fig. 8 (rabbit 261, series 2).—Photograph of an isograft of young ear cartilage with a piece of paper below the metric scale to show the size of the graft before transplantation. During a period of 164 days in the subcutaneous tissues of a nonrelated rabbit it increased in length 78 per cent and in area 300 per cent, which is well above the average for the entire series of isografts.

the nonrelated group. In this series, then, isografts from one breed to another averaged approximately the same increase in size as similar grafts in litter mates.

In 2 instances in which cartilage was exchanged and replaced in the ears there was slightly less growth (53 per cent increase in length and 102 per cent increase in area) than the average for the whole series, notwithstanding the fact that the grafts were undisturbed for 215 days. The transplants in this series were restricted by more fibrous adhesions, with the frequent discovery at autopsy of wrinkling and folding in the grafts. This introduced greater error in their measurement and to a considerable degree accounted for the decreased growth as compared with the autotransplants.

Microscopic Observations: So far as general appearance was concerned, the living cartilage in these sections was similar to that in the autogenous group. Again each graft had a normal basophilic matrix with living cellular elements. In this series, however, there was substantially more fibrous tissue about the transplants, although no absorption or invasion by connective tissue was discovered. Several of the sections showed a mild lymphocytic reaction about the cartilage even after 164 days; lymphocytes were not seen in the autogenous group.

In contrast to the preceding group of autogenous grafts, several localized areas of necrosis were found, and staining variations in the matrix appeared more frequently. In sections of 4 transplants, 215 days old or more, there were unmistakable small areas of bone formation (fig. 9.) Three of these were in the cartilage while the other was adjacent to it, but there was no other calcification. Also, there were some cellular elements of bone marrow about the trabeculations of this osteoid tissue. As in the preceding series, only fibrous tissue united the graft to the bordering cartilage of the ear, with no true bridging by cartilaginous cells.

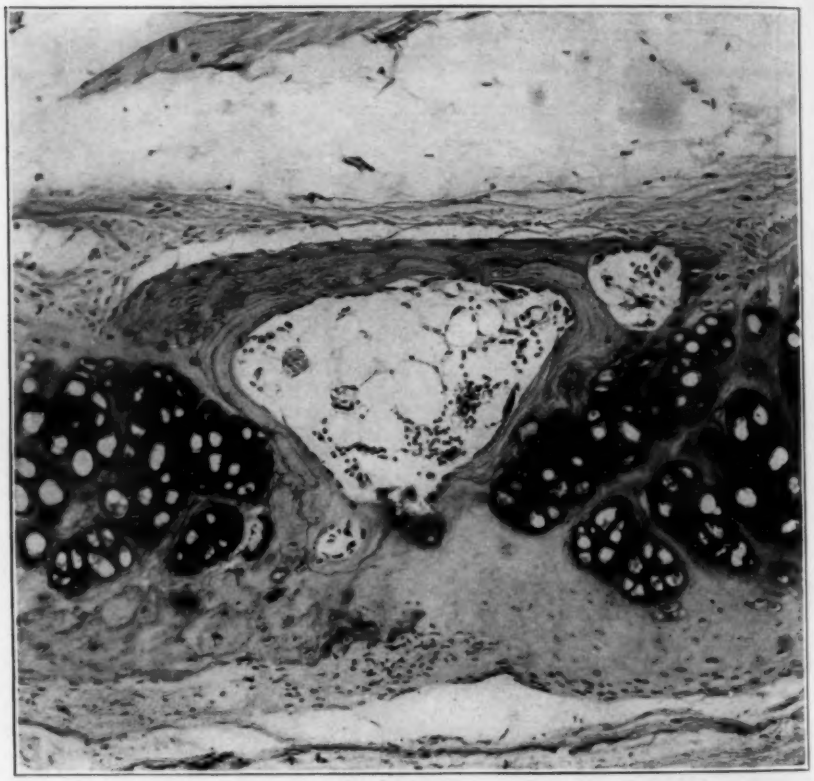


Fig. 9 (rabbit 319, series 2).—Photomicrograph showing formation of osteoid tissue in an isotransplant of young ear cartilage which had been buried in the subcutaneous tissues of a rabbit of different breed for 215 days. Degenerating cartilage cells are visible in the lower central portion, and immediately above are cellular elements of bone marrow.

TABLE 2.—*Results in Second Series*

Position of Graft	Number and Breed of Rabbit	Age at Operation, Days	Duration of Experiment, Days	Weight, Gm.		Ear Length, Cm.		Per Cent Increase in Ear Length	Size of Graft, Cm.		Per Cent Increase in Length of Graft	Per Cent Increase in Area of Graft
				Operation	Autopsy	Operation	Autopsy		Operation	Autopsy		
Subcutaneous	307 (White)	24	40	280	1,100	5.1	9.7	90	1.2 × 0.5	1.5 × 0.9	25	125
Subcutaneous	308 (White)	24	219	325	2,700	5.1	11.5	126	1.4 × 0.45	2.8 × 1.0	100	323
Subcutaneous	298 (Chinchilla)	16	223	230	2,235	4.1	11.0	163	2.0 × 1.35	2.2 × 1.9	10	55
Subcutaneous	300 (Chinchilla)	16	128	230	.....	4.0	10.0	150	1.8 × 1.5	3.0 × 2.8	67	215
Subcutaneous	273 (Chinchilla)	23	94	310	1,475	5.5	11.0	100	1.15 × 0.7	1.6 × 1.15	39	129
Subcutaneous	263 (Chinchilla)	23	106	330	1,055	5.5	10.0	82	1.4 × 0.6	2.4 × 1.0	72	186
Subcutaneous	261 (Dutch)	18	164	275	1,485	4.0	8.8	120	2.8 × 0.8	5.0 × 1.8	78	300
Subcutaneous	262 (Chinchilla)	18	164	325	2,350	5.1	11.5	125	2.6 × 0.6	4.2 × 1.0	62	169
Subcutaneous	319 (White)	21	215	365	2,425	6.0	10.2	70	0.9 × 0.45	1.6 × 0.8	78	157
Subcutaneous	320 (Dutch)	17	215	265	1,515	4.0	8.3	107	0.8 × 0.7	1.3 × 1.1	63	155
Subcutaneous	319 (White)	21	215	365	2,425	6.0	10.2	70	0.8 × 0.7	1.1 × 0.9	37	76
Subcutaneous	320 (Dutch)	17	215	265	1,515	4.0	8.3	107	0.8 × 0.75	1.2 × 0.9	50	80
Ear	319 (White)	21	215	365	2,425	6.0	10.2	70	0.6 × 0.65	0.9 × 0.8	50	85
Ear	320 (Dutch)	17	215	265	1,515	4.0	8.3	107	0.7 × 0.5	1.1 × 0.7	57	120
General average	14 grafts	20	173	...	.....	...	....	107	.....	.....	56	155
Litter mates, average	6 grafts	21	135	...	.....	...	....	109	.....	.....	52	172
Nonrelated, average	6 grafts	19	198	...	.....	...	....	100	.....	.....	61	156
Ear, average	2 grafts	19	215	...	.....	...	....	88	.....	.....	53	102

Both grossly and microscopically many of these isografts showed a greater tendency to wrinkle and fold on themselves during growth. The constrictive action of the increased mass of fibrous tissue seen macroscopically and microscopically may afford an explanation of this observation. The gross appearance of these transplants, except for the presence of a greater number of adhesions, was identical with that of the previous living autografts.

The discrepancy between the average increase in length of the control ear in this group (107 per cent) and in the autogenous series (128 per cent) was probably the result of several factors. For the isografts the animals at operation

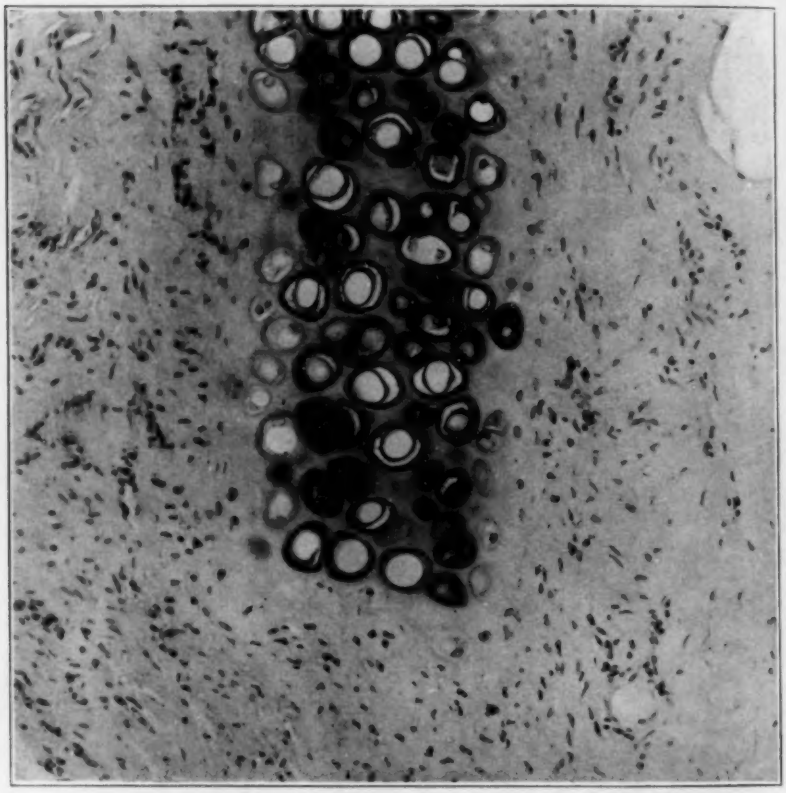


Fig. 10 (rabbit 263, series 3).—Photomicrograph of an adult ear cartilage isograft surrounded by fibrous tissue, showing a cross section of one cut edge. Despite transplantation for 106 days in the subcutaneous tissues of a young rabbit the cut end remains square and no proliferation of young cartilage cells is seen. This presents a striking contrast to the young cartilage graft of figure 6.

were, on an average, 3 days older, at a period when the ear grows rapidly, and several more rabbits of the smaller (Dutch) breed were employed. These factors, combined with a certain experimental error, may account for the apparent reduced growth in the control ears of this series.

An incidental observation of interest was found in most of the donor ears. The cartilaginous defects after removal of the grafts increased in length and area at about the same rate as did normal ears. The cut edges remained sharp, with no visible cartilaginous repair in these large spaces.

Series 3: Isotransplants of Adult Ear Cartilage into Young Rabbits.—Procedure: A small group of transplants was studied to determine the possibility of growth in adult cartilage transplanted to young animals. The rabbits employed were 18 to 24 days old. In 4 instances measured grafts of the mother's ear

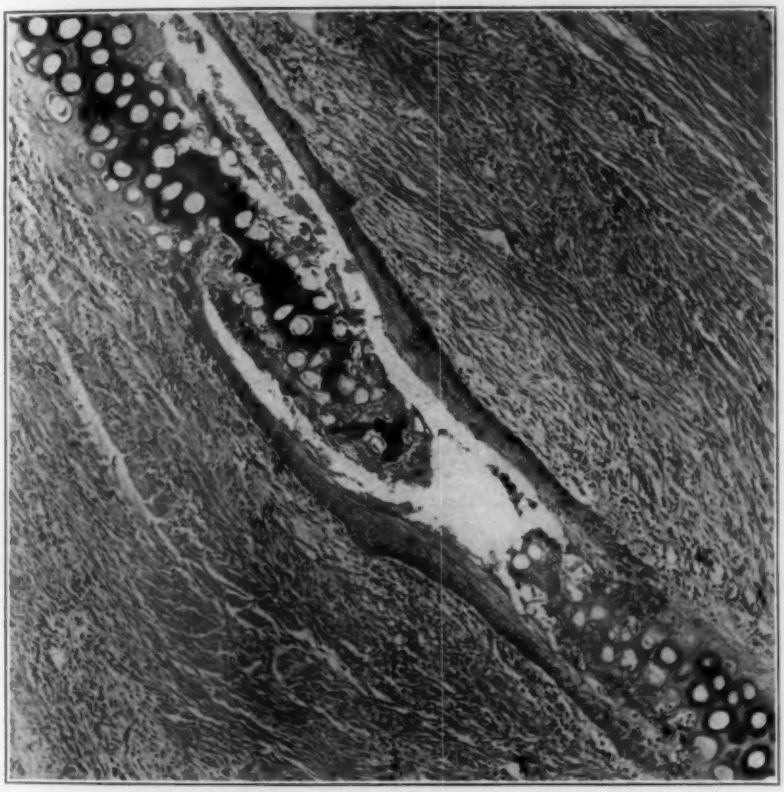


Fig. 11 (rabbit 307, series 3).—Photomicrograph of an ear cartilage graft which shows an implantation cyst separating the ends of the broken cartilage plate. Epithelial cells have advanced along the border of the cartilage.

cartilage were sutured into openings in the cartilage (of the same size and shape) in the ears of the young rabbit. Using the subcutaneous tissues of the back in the same animals, 4 similar portions of the mother's ear cartilage were inserted. For comparison, 2 pieces of ear cartilage from an adult rabbit not related to the young hosts (and of different breed in 1 case) were placed beneath the skin of the back in these young animals. Finally, as a corollary, 2 sections of young ear cartilage were inserted subcutaneously into an adult animal of a different strain. The wounds healed well, and no infections occurred.

TABLE 3.—*Results in Third Series*

Position of Graft	Number and Breed of Rabbit	Origin of Graft	Age at Operation, Days	Duration of Experiment, Days	Weight, Gm.		Ear Length, Cm.		Per Cent Increase in Ear Length	Size of Graft, Cm.		Per Cent Increase in Length of Graft
					Operation	Autopsy	Operation	Autopsy		Operation	Autopsy	
Ear.....	307 (White)	Mother's ear	24	40	280	1,100	5.1	9.7	90	1.4 × 0.45	1.4 × 0.4	No change
Subcutaneous.....	307 (White)	Mother's ear	24	40	280	1,100	5.1	9.7	90	1.5 × 0.9	1.45 × 0.95	No change
Ear.....	308 (White)	Mother's ear	24	219	325	2,700	5.1	11.5	126	1.2 × 0.5	1.2 × 0.5	No change
Subcutaneous.....	308 (White)	Mother's ear	24	219	325	2,700	5.1	11.5	126	1.45 × 0.95	1.5 × 0.9	3
Ear.....	273 (Chinchilla)	Mother's ear	23	94	310	1,475	5.5	11.0	100	1.4 × 0.6	1.5 × 0.4	7
Subcutaneous.....	273 (Chinchilla)	Mother's ear	23	94	310	1,475	5.5	11.0	100	1.5 × 1.05	1.5 × 1.1	No change
Ear.....	263 (Chinchilla)	Mother's ear	23	106	330	1,055	5.5	10.0	82	1.15 × 0.7	0.9 × 0.4	Decrease
Subcutaneous.....	263 (Chinchilla)	Mother's ear	23	106	330	1,055	5.5	10.0	82	1.4 × 1.15	1.4 × 1.15	No change
Subcutaneous.....	261 (Dutch)	Adult white	18	164	...	1,485	4.0	8.8	120	2.5 × 1.3	2.5 × 1.3	No change
Subcutaneous.....	262 (Chinchilla)	Adult white	18	164	...	2,350	5.0	11.5	130	2.1 × 1.3	1.7 × 1.2	Decrease
Subcutaneous.....	317 (Dutch)	21 day old chinchilla	210	55	...	.....	...	....	...	1.3 × 0.8	2.4 × 1.4	85
Subcutaneous.....	317 (Dutch)	21 day old chinchilla	210	55	...	.....	...	....	...	0.9 × 0.9	1.5 × 1.1	66
Subcutaneous.....	318 (White)	21 day old chinchilla	210	55	...	.....	...	....	...	1.35 × 1.1	Lost inf.	..
Subcutaneous.....	318 (White)	21 day old chinchilla	210	55	...	.....	...	....	...	0.9 × 0.9	2.1 × 1.7	133
Adult, average....	10 grafts	.....	22	125	...	.....	...	....	105	.....	.....	No change
Young, average...	4 grafts	.....	210	55	...	.....	...	....	...	.....	.....	95

Results: After an average period of 125 days, the 10 specimens of adult cartilage exhibited no measurable increase in size. At the same time only 2 grafts had diminished definitely in size from gross absorption. Some of these pieces were softer than the previously observed young cartilage grafts, and several had assumed a brownish color suggestive of reduced vitality. All were surrounded by adherent scar tissue, and there were some wrinkling and folding of the edges. The 4 transplants placed in ear defects had maintained their original size only, while the adjacent young cartilage in its efforts to expand was constricted into folds and corrugations along the borders of the graft.

In direct contrast, we found excellent growth in the young transplants buried in adult rabbits of a different breed. In 55 days there was a 95 per cent increase in length and a 223 per cent increase in area. As had been anticipated, demonstrable growth in a transplant depends primarily on the age of the cartilage and not on the age of the host tissues.

Microscopic Observations: Each section of adult cartilage contained well stained matrix, fewer but well preserved cells and a thinner intact perichondrium. There were several localized areas of degeneration, and in 1 section apparent absorption with replacement by fibrous tissue had taken place. On the whole, this adult cartilage was well preserved but showed practically no growth activity at the cut edges. In contrast to the cartilage in young grafts, its sharp, square edges were not covered with proliferating perichondrium, although an abundance of fibrous tissue was present around the grafts (fig. 10).

Two implantation cysts were discovered (fig. 11) and one area of localized osteoid tissue was observed, but again there was no calcification of cartilage. In 2 grafts of adult cartilage placed into window-like defects of the young ear an actual bridging of the gap by new cartilage cells was seen for the first time. The greater portion of this proliferation seemed to arise from the adjacent young cartilage. Henle [48] (1907), while transplanting cartilage from rabbits' ears, had observed this same type of bridging by young cartilage cells. In the 2 adult grafts in which there was gross absorption, the remaining cartilage was living but surrounded by an increased amount of connective tissue. One area of apparent metaplasia of fibrous tissue into cartilage was discovered in this section.

The microscopic appearance of the young cartilage grafts in this series was not unusual except for a considerable lymphocytic infiltration in 1. In the other there was so much constriction from the dense fibrous tissue capsule about the graft that the cartilage had folded back on itself in its effort to expand.

Series 4: Autotransplants and Isotransplants of Rib Cartilage into Young Rabbits.—Procedure: In rabbits 12 to 18 days old, 4 measured portions of costal cartilage were transplanted to the subcutaneous tissues of the abdomen as autografts. Two pieces of rib cartilage were dissected free and then returned to the donor area, and 2 further pieces were implanted beneath the skin of the abdomen as isografts in nonrelated rabbits. Also, a mass of perichondrium scraped from a costal cartilage was buried beneath the skin.

Results: After a period of 133 days (average), 3 of the 4 autotransplants increased in length by 30 per cent. The remaining graft had been broken into two irregular pieces, with indication of slight absorption about the rounded ends. In the case of autografts left in place in the thoracic cage definite identification of the resected piece was impossible, for depressed irregular reconstruction with cartilaginous union had occurred. The 4 isografts showed but 22 per cent increase

48. Henle, A.: Zur Technik der Nasenplastik, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1907, supp. 3, p. 161.

TABLE 4—*Results in Fourth Series*

Position of Graft	Number and Breed of Rabbit	Age at Operation, Days	Duration of Experiment, Days	Weight, Gm.		Per Cent Increase in Weight	Size of Graft, Cm.		Per Cent Increase in Length
				Operation	Autopsy		Operation	Autopsy	
Autotransplants									
Subcutaneous	309 (Chinchilla)	18	217	340	2,700	694	0.8 × 0.15	1.10 × 0.2	38
Subcutaneous	310 (Chinchilla)	18	49	320	1,170	265	0.85 × 0.2	broken	..
Subcutaneous	309 (Chinchilla)	18	217	340	2,700	694	0.75 × 0.2	1.05 × 0.2	40
Subcutaneous	310 (Chinchilla)	18	49	320	1,170	265	0.75 × 0.15	0.85 × 0.1	13
Donor site	315 (White)	16	49	285	800	181	0.9 × 0.2	?	..
Donor site	315 (White)	16	49	285	800	181	1.25 × 0.2	?	..
Donor site	316 (White)	16	210	270	2,720	901	1.25 × 0.2	?	..
Donor site	316 (White)	16	210	270	2,720	901	1.2 × 0.2	?	..
Isotransplants									
Subcutaneous	313 (Dutch)	12	208	360	1,605	346	1.4 × 0.25	1.7 × 0.25	21
Subcutaneous	314 (White)	16	208	530	2,745	418	1.2 × 0.18	1.4 × 0.2	17
Subcutaneous	313 (Dutch)	12	208	360	1,605	346	1.4 × 0.2	1.8 × 0.25	28
Subcutaneous	314 (White)	16	208	530	2,745	418	1.05 × 0.18	1.3 × 0.2	24
General average	4 autografts	17	133	...	.....	479	.....	.....	30
General average	4 isografts	14	208	...	.....	382	.....	.....	22

TABLE 5.—*Results in Fifth Series*

Position of Graft	Number and Breed of Rabbit	Method of Fixing	Age at Operation, Days	Duration of Experiment, Days	Weight, Gm.		Size of Graft, Cm.		Result
					Operation	Autopsy	Operation	Autopsy	
Autotransplants (Ear Cartilage)									
Subcutaneous	315 (White)	Alcohol	16	55	285	800	0.9 × 0.8	0.3 × 0.6	Partial absorption
Subcutaneous	315 (White)	Merthiolate	16	55	285	800	1.0 × 0.8	0.9 × 0.4	Partial absorption
Subcutaneous	315 (White)	Freezing	16	55	285	800	0.6 × 0.6	0.5 × 0.55	Partial absorption
Subcutaneous	316 (White)	Alcohol	16	216	270	2,720	1.8 × 0.4	1.0 × 0.4	Partial absorption
Subcutaneous	316 (White)	Merthiolate	16	216	270	2,720	1.65 × 0.5	Absorbed	Absorbed
Subcutaneous	316 (White)	Freezing	16	216	270	2,720	0.8 × 0.65	Absorbed	Absorbed
Isotransplants (Ear Cartilage)									
Subcutaneous	313 (Dutch)	Alcohol	12	216	223	1,605	0.8 × 0.85	0.5 × 0.4	Partial absorption
Subcutaneous	313 (Dutch)	Merthiolate	12	216	223	1,605	0.9 × 0.7	Absorbed	Absorbed
Subcutaneous	313 (Dutch)	Freezing	12	216	223	1,605	1.0 × 0.65	1.0 × 0.6	Partial absorption
Subcutaneous	314 (White)	Alcohol	16	216	280	2,745	0.7 × 0.5	Absorbed	Absorbed
Subcutaneous	314 (White)	Merthiolate	16	216	280	2,745	0.7 × 0.65	Absorbed	Absorbed
Subcutaneous	314 (White)	Freezing	16	216	280	2,745	0.5 × 0.4	Absorbed	Absorbed
Isotransplants (Rib Cartilage)									
Subcutaneous	317 (Dutch)	Alcohol	24	243	325	1,500	1.25 × 0.1	0.5 ×	Partial absorption
Subcutaneous	317 (Dutch)	Merthiolate	24	243	325	1,500	1.15 × 0.2	1.10 ×	Reduction
Subcutaneous	317 (Dutch)	Freezing	24	243	325	1,500	1.15 × 0.2	Broken	Reduction
Subcutaneous	318 (White)	Alcohol	28	243	285	2,100	0.85 × 0.1	0.4 ×	Partial absorption
Subcutaneous	318 (White)	Merthiolate	28	243	285	2,100	0.8 × 0.2	Broken	Reduction
Subcutaneous	318 (White)	Freezing	28	243	285	2,100	0.8 × 0.2	Last fragment	.....

in lengths in 208 days, but this difference is less striking than that observed in ear cartilage grafts.

Microscopic Observation: There was no essential difference in the microscopic picture of autografts and isografts, for in all cases the cartilage appeared normal and living. The sharp cut ends of each graft had been rounded as the perichondrium had grown over the edge and proliferation had followed. There was an area of bone formation within the cartilage of 1 graft, but in none was there further calcification. Also, in 3 instances there was union of two portions of chondral tissue by new young cartilage. The mass of perichondrium which had been implanted for 49 days produced two distinct areas of young cartilage surrounded by normal perichondrium. Active proliferation of young cartilage tissue was observed in these regions.

On the whole, these observations for hyaline rib cartilage substantiate those for elastic ear cartilage.

Series 5: Autotransplants and Isotransplants of Preserved Ear Cartilage in Young Rabbits.—Procedure: The three methods employed to fix or preserve the grafts for twelve day periods were as follows: (*a*) 95 per cent alcohol; (*b*) a solution of one part aqueous merthiolate to four parts physiologic solution of sodium chloride (O'Connor) and (*c*) refrigeration of the graft for five days in a moist saline sponge followed by rapid freezing and dehydration by a method similar to the procedure for quick freezing of foods.

Six measured ear cartilage autografts, 6 similar isografts from nonrelated rabbits and 6 portions of costal cartilage were treated by the aforementioned three methods, a pair of grafts being used for each. After twelve days they were transplanted into subcutaneous tissues. One section of rib cartilage, preserved by freezing, was extruded from an infected wound.

Results: After an average period of 232 days, every graft showed gross reduction in size with varying amounts of absorption. In some cases cartilage could not be found, and in others the remaining bits could not be measured accurately, which indicated that all three methods gave equally unsatisfactory results.

Microscopic Observations: All sections had dead, degenerating cartilage with no areas of living cells or regeneration. In most instances there were only fragments of pale, ghostlike cartilage structure, and fibrous tissue actively invaded these portions. Several areas of calcification were present (fig. 13), and early osteoid tissue was discovered in one region (fig. 12). The cellular structure showed granular cytoplasm with acidophilic, faded nuclei and karyolysis. There was one notable difference between these two types of grafts: Whereas the preserved ear cartilage was actively invaded and absorbed, the costal cartilage, although dead, resisted fragmention and degeneration rather well during a period of 243 days. This may indicate that preserved hyaline cartilage withstands active absorption for longer periods than does elastic cartilage. However, the difference in physical shape and mass in these two types of transplants as they are exposed to the action of the host tissues probably plays an important role in rapidity of destruction.

Series 6: Isotransplants and Heterotransplants of Preserved Rib Cartilage into Adult Rabbits.—Procedure: Twelve portions of rib cartilage from adult rabbits and 12 similar pieces from adult dogs were implanted in the subcutaneous tissues of rabbits of a different breed. Four sections from each animal were buried in rabbits as fresh grafts used for controls, and the remaining portions, after equal division, were fixed for five days by each of the three methods used in series 5.

Specimens were removed for histologic examination at 7, 14 and 21 day intervals, and the final group was recovered at the time of autopsy.

Object: As Loeb[38] has claimed there is more toxic effect on the part of tissues toward heterotransplants than toward isotransplants, this series was included to observe the effect of different methods in fixation of cartilage grafts on the early host tissue reaction. It was considered possible that fixation might diminish those characteristics of heteroplastic cartilage which invite increased injurious action on the part of the host tissues.

Fig. 12 (rabbit 313, series 5).—Photomicrograph of an isotransplant of young ear cartilage preserved in alcohol before implantation into the subcutaneous tissues of a young rabbit for 216 days. The dead shadow-like cartilage structure includes a localized area of osteoid tissue near the center.

Microscopic Observations: Unfortunately the 21 day sections were ruined during preparation; so the height of the lymphocytic reaction (Loeb[38]) could not be studied.

From an estimation of the marked lymphocytic reaction in the sections of 7 and 14 days, preserved heterografts still produce a more intense reaction in sur-

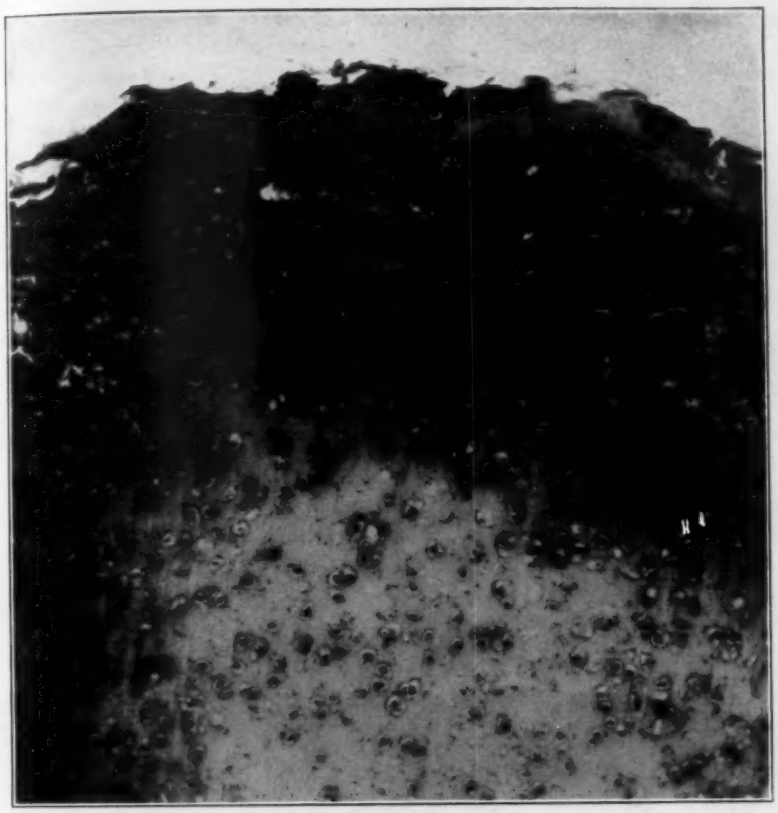


Fig. 13 (rabbit 317, series 5).—Photomicrograph of a cross section of young rib cartilage, preserved by the freezing method, which had been transplanted into a growing rabbit for 243 days. Calcification is apparent in a large portion of the graft, with superficial fragmentation of the periphery.

TABLE 6.—*Results in Sixth Series*

Position of Graft	Number and Breed of Rabbit	Method of Fixing	Estimation of Lymphocytic Reaction			
			7 Days	14 Days	21 Days	Autopsy
Isografts of Rib Cartilage from Adult Chinchilla Rabbit						
Subcutaneous	298 (Chinchilla)	Fresh	++	++++	Sections poorly fixed	+ (114 days)
Subcutaneous	273 (Chinchilla)	Alcohol	+++	++	Sections poorly fixed	Died 23 days
Subcutaneous	263 (Chinchilla)	Merthiolate	++	+	Sections poorly fixed	+ (34 days)
Subcutaneous	263 (Chinchilla)	Freezing	++++	++	Sections poorly fixed	++ (34 days)
Heterografts of Rib Cartilage from Adult Dog						
Subcutaneous	298 (Chinchilla)	Fresh	+++++	++++	Sections poorly fixed	++ (114 days)
Subcutaneous	300 (Chinchilla)	Alcohol	++++++	++++	Sections poorly fixed	++ (50 days)
Subcutaneous	273 (Chinchilla)	Merthiolate	++++	++++	Sections poorly fixed	Died 23 days
Subcutaneous	300 (Chinchilla)	Freezing	++++	+++++	Sections poorly fixed	++ (50 days)

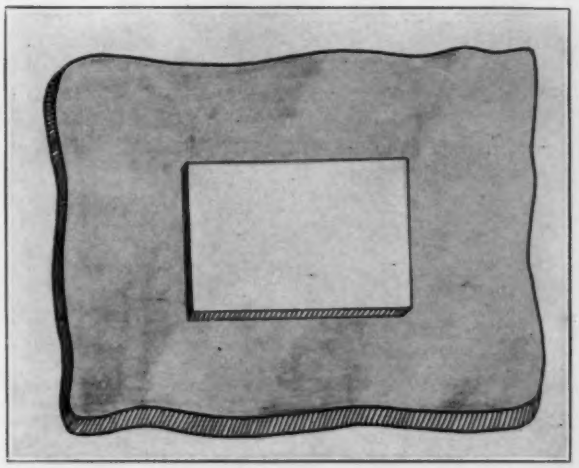


Fig. 14.—Illustration, drawn to scale, showing the average increases of 122 per cent in length and 413 per cent in area of the young ear cartilage autografts in series 1 during a period of 140 days.

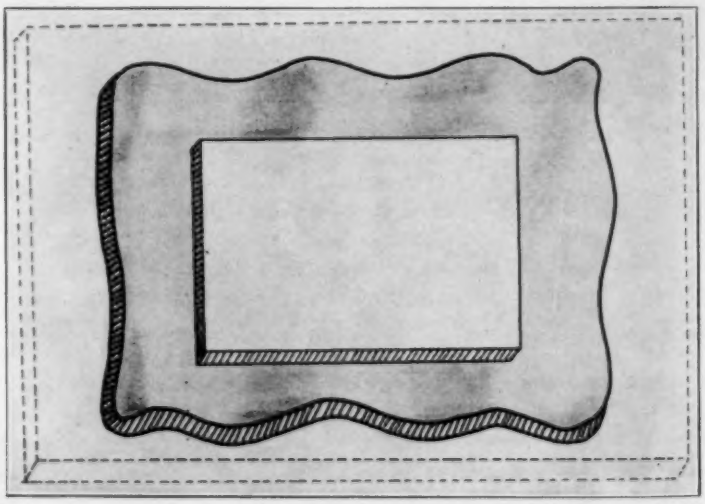


Fig. 15.—Illustration, drawn to scale, representing the average growth of the isotransplants of young ear cartilage in series 2. The original size of the graft is shown in the center, and the outer rectangle of broken lines indicates the calculated or expected growth. The grafts averaged an increase of 56 per cent in length and 155 per cent in area.

rounding tissues than do fixed isografts of cartilage. After 114 days the portion of fresh rabbit control was living and not fragmented by fibrous tissue. The corresponding control of fresh dog cartilage after the same period showed cystic degeneration, with no viable cartilage cells.

CLINICAL APPLICATION OF YOUNG CARTILAGE TRANSPLANTS

In reconstructive surgery fresh human cartilage grafts have been used successfully for many years, but these transplants have consisted mainly of adult cartilage, in which the growth factor is excluded. Recently the importance of correcting certain acquired or congenital deformities during childhood in order to avoid any unfortunate psychopathic sequelae has been recognized. For children whose disfigurement is a marked depression of the nasal bridge, the simplest corrective procedure would employ preserved cartilage. A more satisfactory result might be assured with a fresh transplant of rib cartilage from one parent, but either procedure would probably necessitate the insertion of a larger graft when the child was grown. Therefore, despite the increased operative procedure involved in securing autogenous rib cartilage, the prospect of a permanent transplant which would increase in size with the growth of the nose is an important consideration. When the problem is the reconstruction of a congenitally malformed ear, fresh autogenous cartilage as a graft which would keep pace with the growth of the normal ear would be advantageous.

During the cycle of growth the increase in size of the nose is proportionately greater than that of the ear. The estimated size of a rib cartilage graft, therefore, might require a slight overcorrection for the nose, since costal cartilage grows relatively slowly. When a mother sacrifices a portion of her ear for her child, this adult cartilaginous framework, despite its new location in young growing tissues, will never increase in size. Hence, in such cases an even greater overcorrection is required for the two ears to match when the child is grown. For cartilage grafts in children, therefore, the factor of growth in fresh autotransplants merits emphasis and consideration.

SUMMARY

A careful review of the important literature on cartilage transplantation is presented, with divisions into (*a*) experimental studies on fresh cartilage grafts in animals and (*b*) experiments with preserved cartilage.

No reported experiments on actual growth in grafts of permanent nonembryonal cartilage were discovered in the literature.

A detailed description of the technic employed in transplanting 107 separate cartilage grafts into rabbits is given.

The autografts of young ear cartilage in series 1 averaged an increase in length of 122 per cent over a period of 161 days. In all cases growth was substantiated by microscopic observations of living cartilage and by active proliferation of new cartilage cells at the cut edges of the graft.

Autogenous cartilage transplants in muscle increased in size more rapidly than did those buried beneath the skin.

Isografts of young ear cartilage increased in length by 56 per cent over a period of 173 days (average). Isotransplantation between litter mates as compared with rabbits of different breed produced approximately the same percentage of growth. Also, unmistakable proof of viability and proliferation of new cartilage cells was present in all microscopic sections, and in this group four separate areas of osteoid tissue were discovered.

In no instance was any measurable increase in size observed after an average period of 125 days in adult isografts placed in young rabbits. In contrast, young cartilage grafts in adult host tissue grew exceedingly well.

Less rapid increase in length was observed in autotransplants and isotransplants of young rib cartilage, but in every way macroscopic and microscopic observations substantiated the preceding statements on growth in ear grafts.

Before implantation, eighteen transplants of young rib and ear cartilage were preserved for twelve day periods by three different methods. Varying amounts of macroscopic reduction in size occurred in every instance, and all sections demonstrated dead degenerated cartilage structure with some areas of calcification. Microscopically, the rib cartilage transplants resisted absorption much better than did the thin ear grafts.

At 7 and 14 day intervals, heterografts of preserved dog costal cartilage produced a more intense lymphocytic reaction on the part of the host tissues than did isografts of fixed rabbit cartilage.

CONCLUSIONS

1. Both autotransplants and isotransplants of young rabbit cartilage will grow.

2. Isografts of adult ear cartilage do not increase in size even when placed in the tissues of very young rabbits.

3. Cartilage growth depends on intrinsic factors and is not influenced by the age of the surrounding tissues of the host.

4. Transplants of cartilage grow more vigorously in tissues with greater vascularity.

5. If the aforementioned results can be obtained with other experimental animals, they should have a limited but definite clinical application in plastic and reconstructive procedures on children.

Dr. Jerome P. Webster stimulated my interest in this problem and made helpful suggestions. Drs. A. P. Stout and Robert Hill interpreted the microscopic slides.

CAPILLARY PERMEABILITY AND INFLAMMATION IN RABBITS GIVEN HEPARIN

R. H. RIGDON, M.D.
AND
HARWELL WILSON, M.D.
MEMPHIS, TENN.

Observations on the mechanism of capillary permeability and its relation to inflammation have been the basis for a series of papers by one of us. In these it has been shown that the phenomenon considered to be an increase in capillary permeability as indicated by the localization and concentration of trypan blue following an intravenous injection represents a change which apparently occurs in the epithelial cells, connective tissue cells and endothelial cells after either injection or application of any one of many different types of irritants.[1] This increase in permeability represents a temporary change in the cells, as shown by the localization and concentration of trypan blue in the skin of the rabbit for only three hours after the local application of xylene. The greatest quantity of trypan blue localizes in the area where xylene is applied the shortest time before the dye is given.[2]

The time in which trypan blue after an intravenous injection localizes and concentrates in areas of inflammation is not determined by either the presence or the absence of edema and hyperemia. Furthermore, the time in which polymorphonuclear leukocytes appear in the extravascular tissues in areas of inflammation is different from the time in which trypan blue localizes in its greatest quantity in the skin of the rabbit.[3] It is evident from these observations that capillary permeability as shown by the localization and concentration of trypan blue is a phenomenon different from that which permits the localization of polymorphonuclear leukocytes in areas of inflammation.

Aided by grants from the John and Mary R. Markle Foundation and the University of Tennessee.

From the Department of Pathology and the Department of Surgery, the University of Tennessee.

1. Rigdon, R. H.: Relation of Capillary Permeability to Inflammation, South. M. J. **34**:292, 1941.

2. Rigdon, R. H.: (*a*) Capillary Permeability in the Skin of the Rabbit, Proc. Soc. Exper. Biol. & Med. **42**:43-45, 1939; (*b*) Capillary Permeability in Areas of Inflammation Produced by Xylene, Arch. Surg. **41**:101 (July) 1940.

3. Rigdon (footnotes 1 and 2 *b*).

Capillary permeability and inflammation have been studied in narcotized rabbits.[4] Pickrell[4a] in 1938 showed that leukocytes failed to localize about pneumococci in the skin of rabbits intoxicated with ethyl alcohol. Cressman and one of us (R. H. R.)[4b] confirmed these observations. None of these investigators, however, were able satisfactorily to explain this phenomenon. One of us (R. H. R.)[5] has recently shown that epinephrine influences capillary permeability and the localization of leukocytes about foci of bacteria in the skin of the rabbit. It has been suggested that vascular constriction may explain these observations when epinephrine is used.

The mechanism of vascular changes and of chemotaxis has been studied frequently since the observations of Cohnheim and Metchnikoff. Leukocytes have been described as "sticking" to the endothelial cells in the small blood vessels in areas of inflammation.[6] Present knowledge is meager as regards the changes in the endothelial cells and the mechanism by which leukocytes concentrate in areas of inflammation. Since heparin is an anticoagulant, it was thought that the presence of this substance in large quantities in the blood of the rabbit might influence capillary permeability and the localization of leukocytes in areas of inflammation. This paper is a report of our studies on the effects of heparin[7] on capillary permeability and inflammation in the rabbit.

EFFECT OF HEPARIN ON CAPILLARY PERMEABILITY

Capillary permeability in the normal rabbit may be studied by carefully applying xylene with a cotton applicator to local areas of skin at frequent intervals, after which 10 cc. of a 0.2 per cent solution of trypan blue is given intravenously. This dye localizes first and in greatest quantity in the area of skin where xylene is applied the shortest time before the dye is given. When the interval between the application of xylene and the injection of the dye is three hours or longer, no more dye localizes and concentrates in the xylene-treated areas than in the untreated skin.[2b]

In the present experiment 4 rabbits were used. The skin was carefully shaved twenty-four hours or longer before the xylene was applied. Each animal was given intravenously 4,000 units of heparin. The

4. (*a*) Pickrell, K. L.: The Effect of Alcohol Intoxication and Ether Anaesthesia on Resistance to Pneumococcal Infection, Bull. Johns Hopkins Hosp. **63:** 238, 1938. (*b*) Cressman, R. D., and Rigdon, R. H.: Permeability and Inflammation in Narcotized Rabbits, Arch. Surg. **39:**586 (Oct.) 1939.

5. Rigdon, R. H.: A Study of Capillary Permeability and Inflammation in the Skin of Rabbits Given Adrenalin, Surgery **8:**839, 1940.

6. Clark, E. R., and Clark, E. L.: Observations on Changes in Blood Vascular Endothelium in the Living Animal, Am. J. Anat. **57:**385, 1935.

7. The heparin used in these experiments was supplied to us by Roche-Organon Inc., of Nutley, N. J.

heparin was diluted with equal parts of physiologic solution of sodium chloride. This quantity of heparin prevented the clotting of blood, as is shown by the data:

Rabbit	Quantity of Heparin, Units	Clotting Time, Minutes
560	4,000	50+
561	4,000	45+
562	4,000	35+
563	4,000	25+
A	0	5
B	0	3
C	0	5
D	0	4

(To determine the clotting time of blood, 10 cc. is taken from the heart and 2 cc. is put into each of three test tubes [1 by 10 cm.]. The tubes are inverted each minute during the first twenty minutes and thereafter at five minute intervals. Clotting is complete when the tubes can be inverted without escape of the blood.)

Xylene was applied to the skin three hours, two hours, one hour, thirty minutes and immediately before 10 cc. of a 0.2 per cent solution of trypan blue was injected intravenously. Heparin (4,000 units) was injected intravenously thirty minutes before the injection of the dye. Trypan blue localized and concentrated within five minutes in the last area where xylene had been applied. The dye subsequently localized and concentrated in the other xylene-treated areas of skin. There was a progressive diminution in the quantity of dye in the skin when the interval between the application of the xylene and the injection of the dye was increased. There was no difference either in the time or in the quantity of dye that localized in the xylene-treated areas of skin in rabbits given heparin and in the controls.

EFFECT OF HEPARIN ON THE LOCALIZATION OF STAPHYLOCOCCI IN AREAS OF INFLAMMATION

Staphylococci in suspension in saline solution when given intravenously to rabbits localize and concentrate in xylene-treated areas of skin in a manner similar to the localization of trypan blue.[8] The skin of 6 rabbits was prepared for use in the present experiment. Four of these animals were given intravenous injections of 2,000 units of heparin. The injections were made at forty-five minute intervals. Fifteen minutes after the second injection of heparin, xylene was applied to a local area of the skin and 10 cc. of a saline suspension of staphylococci was injected intravenously. The rabbits were killed one hour after injection of the bacteria. The xylene-treated area of skin was removed from

8. Rigdon, R. H.: Localization of Staphylococci in Areas of Inflammation Produced by Xylene, Arch. Surg. **41**:879 (Oct.) 1940.

each of the 6 animals. The sections of skin were divided, and one part was fixed immediately in a 10 per cent concentration of solution of formaldehyde U. S. P. The second part was put into the incubator at 37.5 C. The tissue was removed after five hours and placed in the solution of formaldehyde. Paraffin sections were prepared and were stained with hematoxylin and eosin.

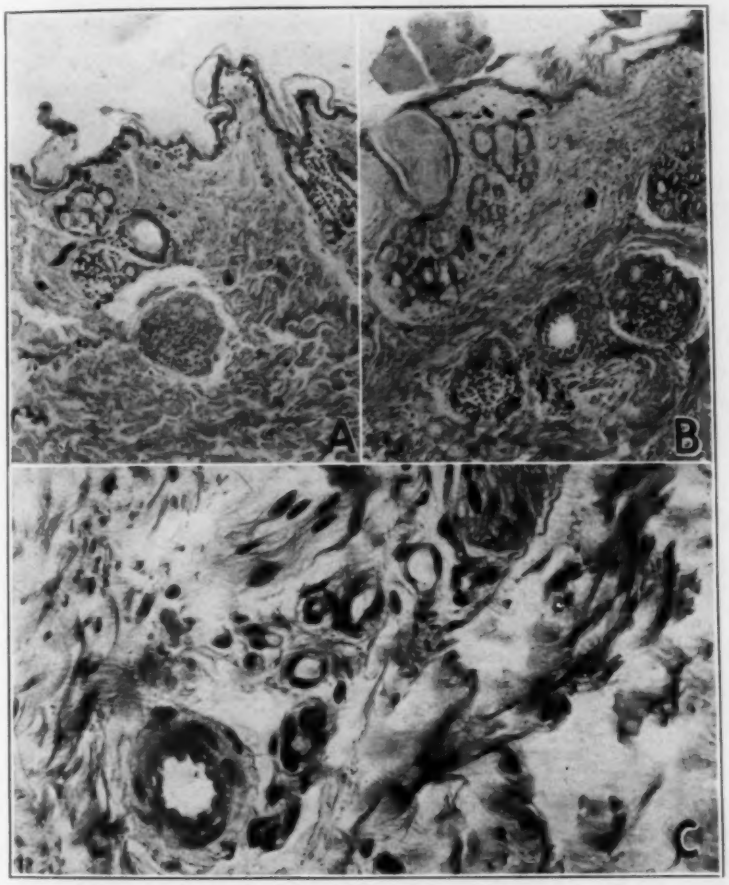


Fig. 1.—Staphylococci after an intravenous injection localize in the small blood vessels immediately below the squamous epithelium in the area where xylene has been applied. *A*, heparin (2,000 units) was given to a rabbit fifteen minutes before the xylene was applied. A saline suspension of staphylococci was given immediately after application of the xylene. *B*, control for *A*. Apparently there is no difference in *A* and *B*. *C*, portion of the same section shown in *B*. Note the absence of bacteria in the lumen of the small vessels in the subcutaneous tissues.

The staphylococci multiply in the lumens of the small blood vessels during incubation, as shown in figure 1. Apparently heparin has no

effect on the localization and concentration of staphylococci in areas of inflammation. Figure 1 *A* shows the accumulation of staphylococci in the small vessels in the corium. Figure 1 *B* shows the reaction in the control. The lumen of every blood vessel in this portion of the skin was not filled. However, we could see no difference in the number of the vessels involved in the experimental and in the control group. (When xylene is applied to the skin and staphylococci are given intravenously, the bacteria localize only in the small vessels immediately beneath the squamous epithelium. Figure 1 *C* is a portion of the section shown in figure 1 *B*. There were several small vessels here, but staphylococci were not present in any of them.)

EFFECT OF HEPARIN ON THE LOCALIZATION OF LEUKOCYTES IN AREAS OF INFLAMMATION

It is evident from the two preceding experiments that heparin when given intravenously does not influence the localization and the concentration of either trypan blue or staphylococci in xylene-treated areas of skin in the rabbit. To study the effect of heparin on the localization of polymorphonuclear leukocytes in areas of inflammation, 9 rabbits were used. Six of these were given intravenously 2,000 units of heparin. This quantity of heparin was injected a second time forty-five minutes later and again forty-five minutes later. Immediately after the first injection of heparin, 0.2 cc. of a heavy saline suspension of staphylococci was injected subdermally into two areas on the side of the abdomen. Three rabbits were used for the controls. All of the rabbits were killed two hours after the injection of the staphylococci. Sections of the skin from the areas into which the organisms had been injected were removed and fixed in a 10 per cent concentration of solution of formaldehyde U. S. P. Histologic preparations were made and stained with hematoxylin and eosin.

There appeared to be less macroscopic inflammation in some of the rabbits given heparin than was present in some of the controls. Microscopic studies showed some variation in the number of leukocytes about the bacteria in both the normal and the heparinized animals. The variation in the number of leukocytes, however, in the two groups was considered insignificant.

It was thought that should heparin have any influence on the localization of leukocytes in areas of inflammation it might become evident if the aforedescribed experiment were carried on for four hours instead of for only two hours. Each of 4 rabbits, therefore, was given intravenously 2,000 units of heparin every forty-five minutes for six injections. Two-tenths cubic centimeter of a heavy saline suspension of staphylococci was injected subdermally immediately after the first injection of heparin. The injection of staphylococci was repeated two hours later. Two rabbits were used for controls. The animals were

killed four and one-half hours after the first injection of heparin. The skin at the site of the bacterial inoculation was removed and fixed in solution of formaldehyde. Histologic preparations were made and stained with hematoxylin and eosin.

There was no apparent difference in the number of leukocytes around the staphylococci in the heparinized rabbits as compared with the controls (fig. 2). A large number of red blood cells were present in the inflammatory area in some of the rabbits to which heparin had been given.

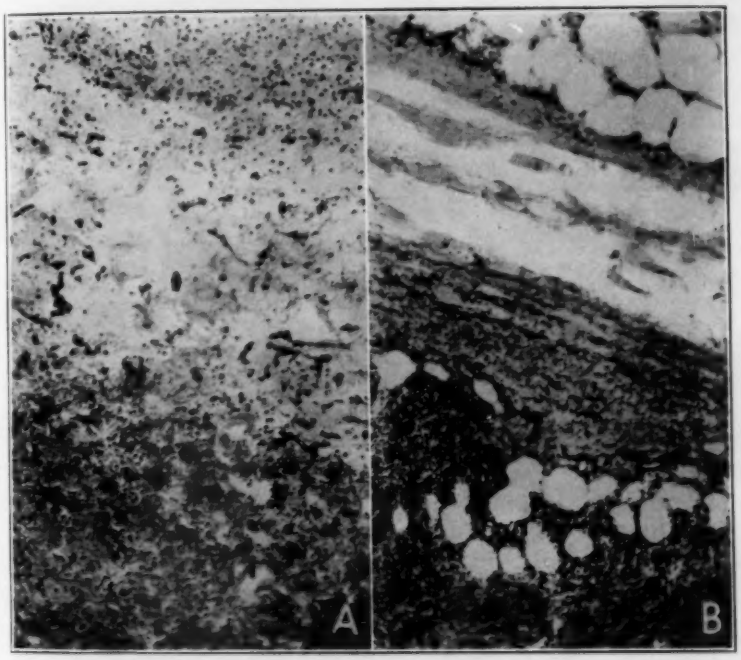


Fig. 2.—Leukocytes localize and concentrate about staphylococci in the skin of the heparinized rabbit in the same way as in a normal animal. *A*, reaction in a normal rabbit four and one-half hours after the subdermal injection of 0.2 cc. of staphylococci. *B*, reaction of rabbit given intravenously a total of 12,000 units of heparin during the interval.

Xylene was applied to the skin of 3 rabbits which had been given heparin to observe the development of the macroscopic evidences of inflammation. These rabbits were given 2,000 units of heparin, and fifteen minutes later xylene was carefully applied to a local area of the skin. The injections of heparin were repeated each forty-five minutes to a total of five injections. Xylene was applied over a second area of skin after the third injection of heparin. Hyperemia and edema occurred fifteen to thirty seconds after the application of xylene. This is the time

in which this change occurs in normal rabbits. From these observations it may be concluded that heparin as used in this experiment does not influence the development of inflammation in the skin of the rabbit.

LOCAL EFFECT OF HEPARIN ON AN INFLAMMATORY REACTION

Heparin when given intravenously over a period of four hours in six equal doses (2,000 units each), as was shown in the previous experiment, apparently has no effect either on the development of macroscopic

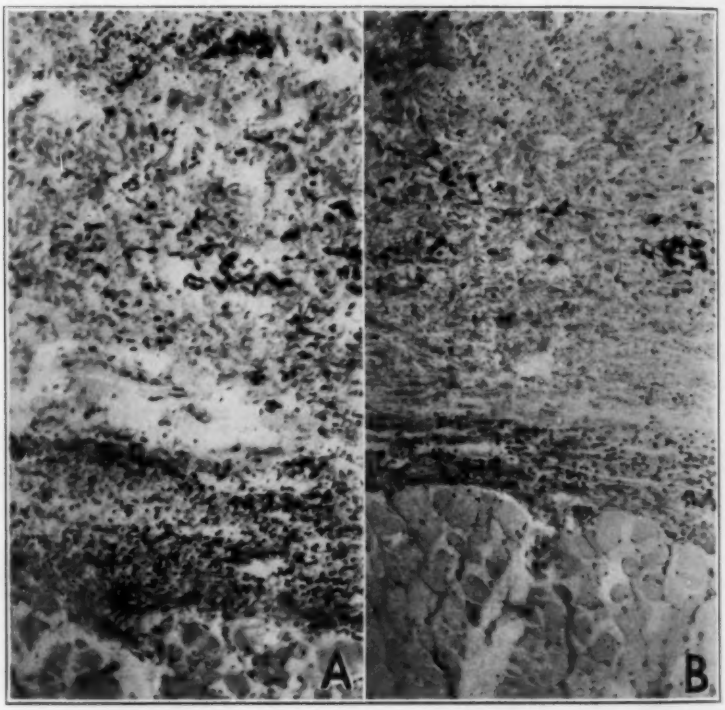


Fig. 3.—The local injection of heparin apparently does not influence the localization of leukocytes about staphylococci. Two-tenths cubic centimeter of staphylococci was injected subdermally on the right and the left side. Two hundred units (0.2 cc.) of heparin was injected into the bleb on the right. This quantity of heparin was injected a second time forty-five minutes later and a third time after an additional forty-five minutes. The rabbit was killed two hours after injection of the bacteria. *A*, leukocytic reaction in a rabbit given saline solution. *B*, reaction in the same rabbit when heparin was given.

inflammation or on the localization of leukocytes about the bacteria. To study the local effect of heparin on the development of inflammation, 6 rabbits were given subdermal injections of 0.2 cc. of a heavy saline suspension of staphylococci into two areas on the right and into two areas on the left side of the abdomen. Immediately after injection of

the bacteria, 0.2 cc. of heparin (200 units) was injected into the two blebs on the right and an equal quantity of saline solution was injected into the two blebs on the left. The injections of heparin and saline solution were repeated after forty-five minutes and were given for a third time forty-five minutes later. The rabbits were killed two hours after injection of the organisms. The areas of cutaneous inflammation were removed and fixed in solution of formaldehyde. Histologic sections were prepared and were stained with hematoxylin and eosin.

Macroscopically there appeared to be a more extensive reaction in the areas treated with saline solution than in those treated with heparin. However, microscopically no difference was observed in the number of leukocytes in the areas treated with staphylococci and saline solution as compared with those treated with staphylococci and heparin in the same rabbit (fig. 3). The individual cells in the inflammatory areas in the two groups of animals were studied to see whether there was any variation in the degree of phagocytosis. Heparin, as far as we could determine from a study of these sections, does not affect the phagocytic activity of leukocytes.

OBSERVATIONS ON CAPILLARY PERMEABILITY IN AREAS OF SKIN TREATED BY INJECTION OF HEPARIN

Capillary permeability has been studied after the intradermal injection of a series of different preparations, such as staphylococci, staphylococcus toxin, horse serum broth, tissue extracts and hypertonic solutions of sodium chloride.[9] Trypan blue localizes and concentrates only during a specific interval where the aforementioned preparations are injected. This interval varies with the different preparations. To study the effect of heparin directly on capillary permeability, 4 rabbits were given intradermal injections of 0.2 cc. of heparin diluted with an equal volume of saline solution (200 units). The heparin was injected two and one-half hours, one hour, thirty minutes and immediately before 10 cc. of a 0.2 per cent solution of trypan blue was given intravenously. Xylene was applied to the skin for a control. The skin was carefully observed for the appearance of the dye. Trypan blue localized and concentrated in the xylene-treated skin in each of the 4 rabbits; however, no dye concentrated in any of the areas into which heparin had been injected.

It is evident from this experiment that heparin as used in these experiments does not affect the permeability of the cells in the rabbit's skin.

---

9. Rigdon, R. H.: Observations on Capillary Permeability in Areas of Inflammation Produced by Staphylococci, Surgery, to be published. Rigdon, R. H., and Haynes, A.: Observations on Capillary Permeability in Skin of Sensitive Rabbits, J. Lab. & Clin. Med., to be published. Rigdon.[2b]

COMMENT

The results of this study show that heparin has no effect on capillary permeability, the development of the macroscopic signs of inflammation or the localization of leukocytes in areas of inflammation. It has been shown by other investigators that heparin has no effect on the content of sugar, calcium, uric acid, nonprotein nitrogen or phosphatase in the blood or on the hemoglobin level, red or white cell count or hematocrit reading. It increases the resistance of red blood cells to hypotonic salt solutions, inhibits glycolysis and alters the sedimentation rate. In addition to these changes, all reactions involving complement may be affected because of the inhibitory action on the complement midpieces.[10]

The observation that heparin does not influence the localization of leukocytes in areas of inflammation appears to be significant. Although the mechanism of chemotaxis is not understood, many investigators have described the process by which leukocytes localize in areas of inflammation as the result of "a sticking of leukocytes to the endothelial cell." The manner by which the endothelial cells acquire this characteristic is not well understood. It is suggested from this study that this "stickiness" is not the same process as that which occurs in the endothelial cells preceding the formation of thrombi.

Murray [10a] has presented evidence that heparin will prevent thrombosis in both the portal and the peripheral circulation. The factors which cause the improvement in phlebitis are not well understood; however, Murray said that with heparin limiting the progressive thrombus the inflammatory reaction to the thrombus already present may burn itself out fairly quickly and the symptoms subside. The effect of heparin on thrombosis appears to be on the platelets. Best and his associates [11] have observed the localization of platelets on a rough area in a glass tube and have prevented this by adding heparin to the blood.

In considering the effect of heparin on phagocytosis it may be stated that some observers have found that phagocytosis in vitro is increased when heparin is substituted for sodium citrate as the anticoagulant. The latter is thought to be toxic for leukocytes.[12] Studies are now in progress in our laboratory on the effect of varying quantities of heparin on phagocytosis in vitro.

The mechanism of the changes in the endothelial cells of the small blood vessels in areas of inflammation has been discussed in another

10. (*a*) Murray, G. D. W.: Heparin in Thrombosis and Embolism, Brit. J. Surg. **27**:567, 1940. (*b*) Plass, E. D., and Rourke, M. D.: A New Procedure for Determining Blood Sedimentation Rates, J. Clin. Investigation **5**:531, 1928.

11. Best, C. H.; Cowan, C., and McLean, D. L.: Heparin and the Formation of White Thrombi, Science **85**:338, 1937.

12. Veazie, L., and Meger, K. F.: Heparin as an Anticoagulant in the Brucella Phagocytic Index Test, Proc. Soc. Exper. Biol. & Med. **32**:1616, 1935.

paper.[1] Lange [13] stated the opinion that the surface tension of the cells in the reticuloendothelial system is changed and that particulate matter sticks to the endothelial cells because of this change in the surface tension.

Mason,[14] in a recent review on heparin, has discussed the effect of this substance on the reticuloendothelial system. He stated:

> Von Jansco has employed heparin in experiments to study the mechanism of reticulo-endothelial blockade by colloidal metals. He has shown that storage of these foreign substances by reticulo-endothelial cells takes place in two phases: (1) adsorption on the surface of the cell facilitated by the previous formation of a fibrin network around the particle and (2) vascular storage of the adsorbed particle in the cell. The preliminary process, therefore, resembles that of coagulation and is inhibited by heparin (and several other anticoagulants). A specific means, therefore, is available for blocking this type of behavior of these cells without poisoning or in any other way diminishing their potential activity.

In the present experiments it has been shown that heparin apparently has no effect on the endothelial cells of the small blood vessels in the skin of the rabbit. The variation in the effect of heparin on the function of the cells of the reticuloendothelial system and the endothelial cells lining the small blood vessels in areas of inflammation is interesting.

SUMMARY

Heparin as used in these experiments has no effect on capillary permeability, the macroscopic development of inflammation or the localization of leukocytes in areas of inflammation.

The phagocytosis of staphylococci by polymorphonuclear leukocytes in vivo apparently is not affected by heparin.

---

13. Lange, F. J.: Role of Endothelium in the Production of Polyblasts in Inflammation, Arch. Path. **1**:41 (Jan.) 1926.

14. Mason, M. F.: Heparin: A Review of Its History, Chemistry, Physiology and Clinical Applications, Surgery **5**:451 and 618, 1939.

EFFECT OF HEPATIC DAMAGE ON GASTRIC ACIDITY

M. H. STREICHER, M.D.
CHICAGO

Individual clinical reports (Stevens;[1] Meakins[2]) are to be found in the literature of decrease or complete absence of gastric acidity in patients with moderate or severe damage to the liver, irrespective of the cause of the damage. One is also familiar with individual analyses of the gastric contents of patients treated for malignant tumor of the stomach or of the kidney in whom large sections of the liver have been damaged secondarily by irradiation; in these studies, too, the recorded values for acidity are definitely lower than the average normal.

It seemed that a systematic study of the effect of damage to the liver on the gastric acidity response was warranted.

PROCEDURE

Dogs were used for these experiments. Damage to the liver was produced experimentally in two ways: (1) by direct high voltage irradiation of the liver and (2) by intragastric administration of carbon tetrachloride in milk. The gastric juice was collected under histamine stimulation by means of a Pavlov pouch (female dogs only) and analyzed.

The experiments with irradiation were performed as follows: The Pavlov pouch was made on the left side of the dog, and control tests of the normal gastric juice were obtained over a substantial period. For direct irradiation the abdomen of the dog was opened under pentobarbital sodium anesthesia; all viscera were blocked off by lead plates, and the liver was exposed to high voltage irradiation for forty-two minutes, the equivalent of three times the skin erythema dose for the human being. The dog received 150 roentgen units each minute. The abdomen was closed, and the gastric acidity was determined at frequent intervals. Each time the values approximated the initial level the experiment was repeated, and this was continued as long as the dog remained in good condition. Biopsy studies were made and blood was drawn for chemical analysis at regular intervals. A complete autopsy was performed on each dog.

From the Department of Medicine, the University of Illinois.

Presented at the Thirteenth Annual Meeting of the Central Society for Clinical Research, Chicago, Nov. 1, 1940.

1. Stevens, A. A.: The Practice of Medicine, Philadelphia, W. B. Saunders Company, 1922, p. 424.

2. Meakins, J. C.: The Practice of Medicine, St. Louis, C. V. Mosby Company, 1940.

In the carbon tetrachloride experiments the solution was administered intragastrically by means of a stomach tube, 1 cc. per 7 pounds (3 Kg.) of body weight three times weekly as long as the dog remained in good physical condition. Studies of the gastric juice, analyses of the blood and analyses of biopsy sections of the liver of each dog were made. A control experiment was performed in which radiation was applied over the muscles of the leg of the dog.

RESULTS

Irradiation.—Table 1 shows a schedule for the dogs treated by direct irradiation.

TABLE 1.—*Schedule of Dogs Treated by Irradiation*

Dog	Date	Weight, Pounds	Duration of Experiment, Months	No. of Treatments *	Dose in Roentgens *	Condition of Dog 24 Hours Before Death	Liver	
							Biopsy	Autopsy
2	12/13/37	26	16	7	35,700	Good	Atrophy	Granular necrosis
13	11/28/38	22	15	10	63,000	Good	Atrophy	Granular necrosis
19	2/22/39	30	19	4 E 6 L	25,200 E. 37,800 L	Good	Atrophy	
20	4/ 5/39	26	15	8	50,400	Good	Atrophy	Granular necrosis
23	3/14/40	26	6	2	12,600	Good	Atrophy	

* E following a number indicates that that number of radiation treatments or of roentgens was applied to the extremity. L following a number indicates that that number of radiation treatments or of roentgens were applied to the liver.

TABLE 2.—*Maximal Acidity (Dogs 2, 13 and 20)*

Dog	Treatments	Before Irradiation		After Irradiation	
		Free Acid, mEq.	Total Acid, mEq.	Free Acid, mEq.	Total Acid, mEq.
2	7	120	152	63.2	100.88
13	9	109.76	121.68	55.0	86.0
20	7	122.0	138.8	62.0	107.0

Gastric Acidity: In dogs 2, 13 and 20 (table 2) changes in the acidity were noted. Within forty-eight to seventy-two hours after each treatment there was evident an initial increase in the gastric acidity (free and total) over the pretreatment level, and then a gradual decrease followed. If additional radiation treatments were administered the acidity curve climbed to the previous level and remained at that point. Subsequent irradiation exaggerated the depression of gastric acidity. With each additional treatment the acidity curve was delayed more and more in its return to a previous level, and in the terminal stage the dog was not only incapable of producing as much acidity as previously but actually produced less. In other words, a definite low level was established. Dogs 19 and 23 are now under observation and have received six and two treatments respectively. In figures 1 and 2 is demonstrated the behavior of gastric acidity after direct irradiation of the liver, expressed in milliequivalents per thousand cubic centimeters of gastric juice.

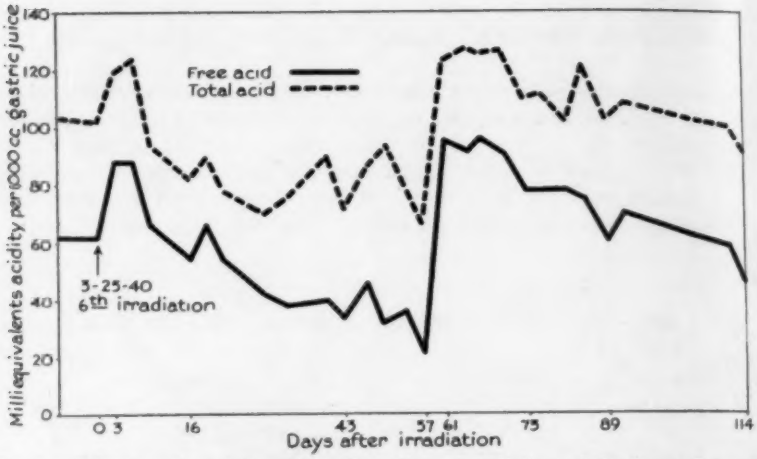


Fig. 1.—Behavior of gastric acidity after direct irradiation of the liver of dog 19.

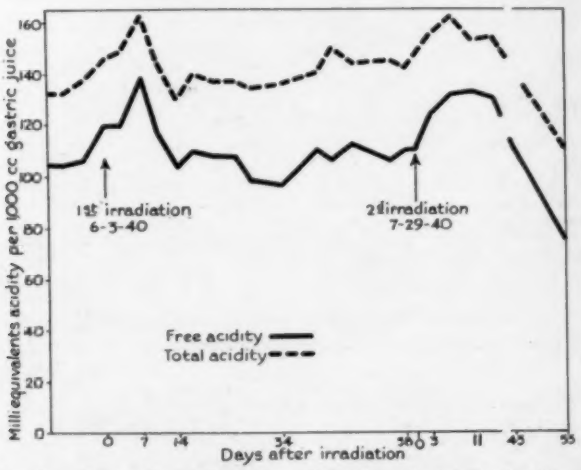


Fig. 2.—Behavior of gastric acidity after direct irradiation of the liver of dog 23.

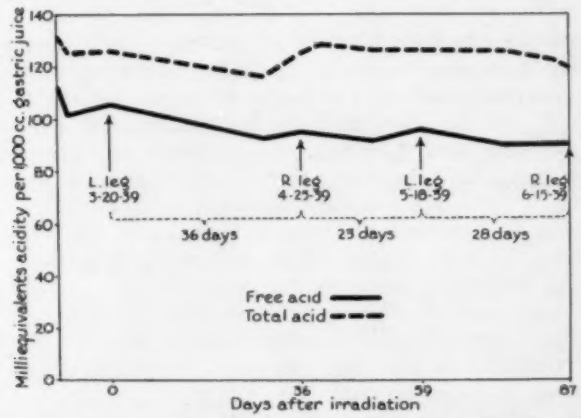


Fig. 3.—Response of gastric acidity to irradiation of the muscles of the extremity (dog 19).

Figure 3 demonstrates the response of acidity to radiation applied to the muscle of the extremity; this experiment was used as a control against irradiation of the liver.

Chemical Studies of Gastric Juice and Blood: These analyses were carried out for a period of four years, throughout the experiments.

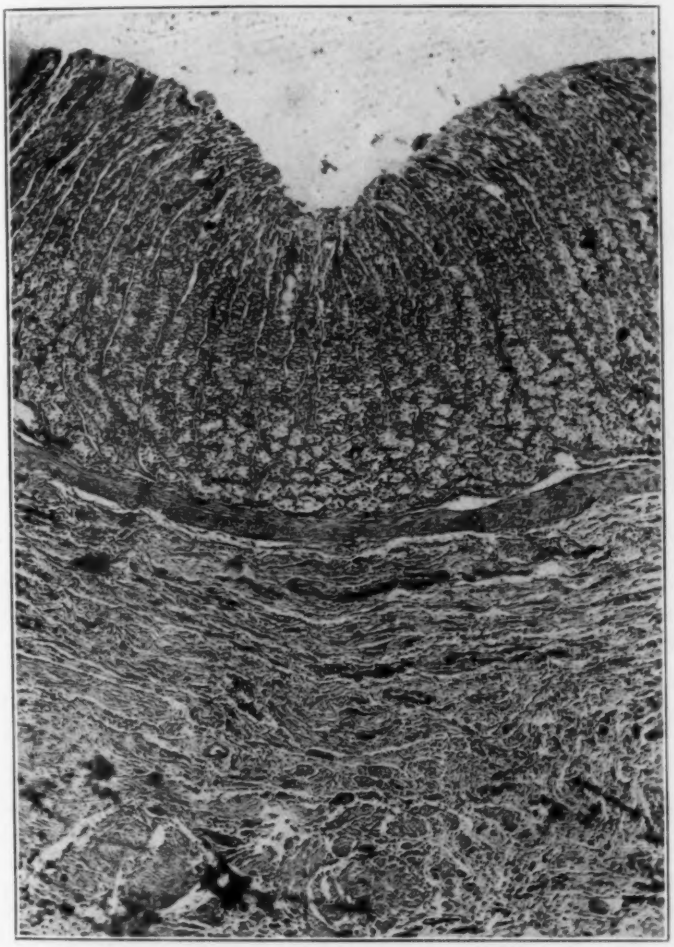


Fig. 4.—Low power photomicrograph of the cellular changes observed. The specimen was taken from the gastric mucosa.

The values for total base and total chlorides did not elicit any demonstrable variations, and the hydrogen ion concentrations failed to parallel the changes in the acidity values. Relative studies are now in progress in the laboratory.

The total proteins averaged about 6 Gm. per hundred cubic centimeters, and the albumin-globulin ratio did not show any inversion. The icterus index was elevated only at the terminal stage.

Stomach (Microscopic Studies): The most prominent changes were in the fundus and in the bed of the stomach. The chief cells showed marked cytolysis

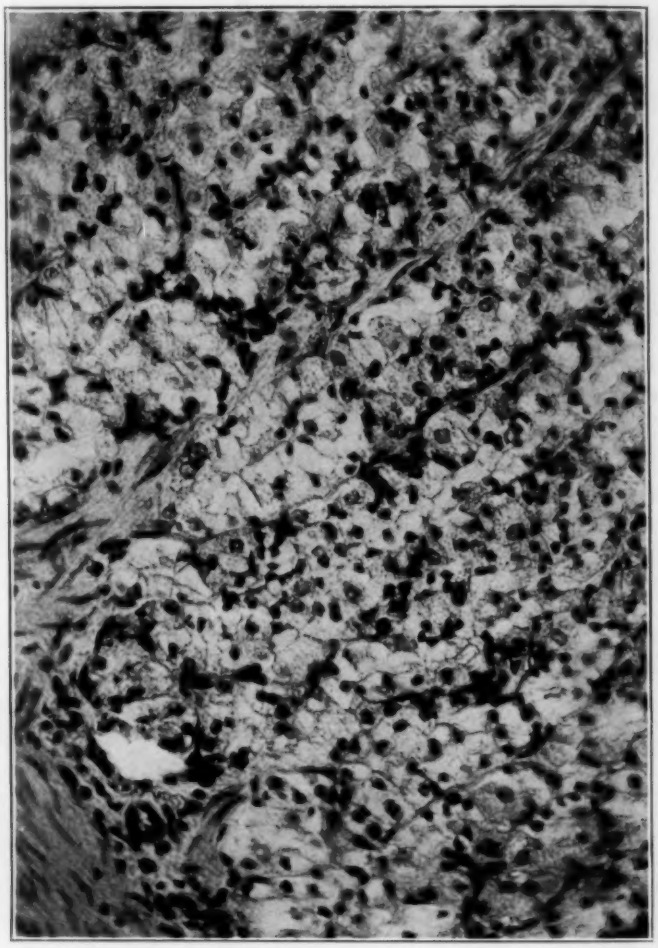


Fig. 5.—High power magnification of the specimen shown in figure 4.

and degeneration; only the nuclear structure remained intact. The epithelial cells also showed marked transitional changes, from a columnar to a cuboidal type of cell. The gland structure was markedly distorted, and the cell structure showed evidence of degeneration. The glands were widely separated.

There were some lymphocytic infiltration and fibrosis in the submucosa. The parietal cells were not altered to any marked degree.

In general, the picture described is characteristic of degenerative changes.

Figures 4 and 5 show the cellular changes observed in our experiments; this slide was taken from the fundus of dog 2 at autopsy (fifteen minutes after death)

Fig. 6.—Photomicrograph of a specimen taken from the fundus of the stomach of a normal dog.

and demonstrates a portion of the gastric mucosa under low and high power. Note the picture of the fundus of a stomach of a normal dog (fig. 6) for comparison.

Liver: An autopsy analysis of dogs 2, 13 and 20, examined post mortem on March 23, 1939, on March 22, 1940 and on Aug. 7, 1940 respectively revealed the following data:

Fig. 7.—Photograph of the liver of a dog treated by irradiation.

Fig. 8.—Photomicrograph of liver tissue.

Fig. 9.—Dog 19. Note the denuded areas on the extremity, due to irradiation.

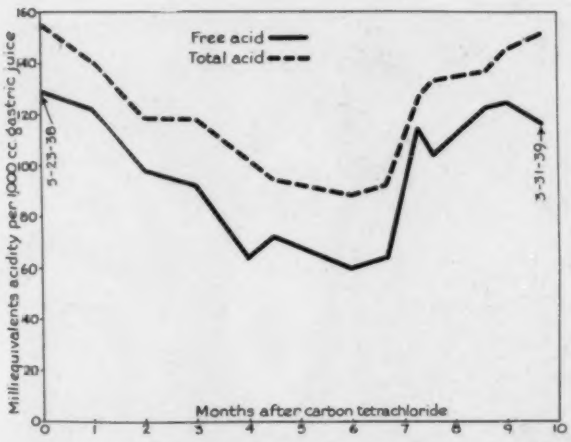


Fig. 10.—Response of gastric acidity to administration of carbon tetrachloride (dog 7).

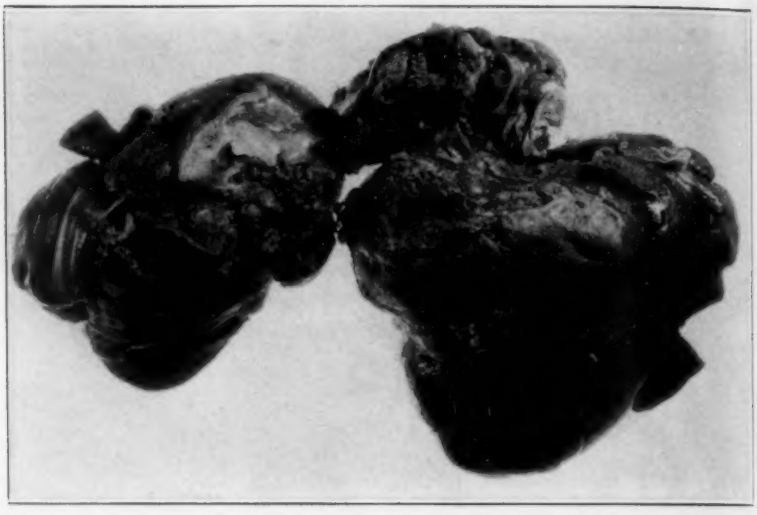


Fig. 11.—Photograph of the liver of a dog given carbon tetrachloride.

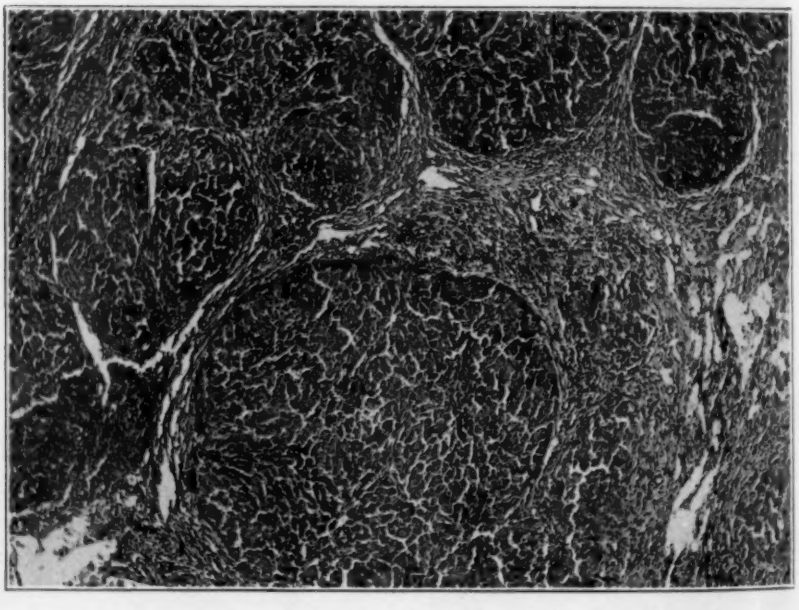


Fig. 12.—Photomicrograph of liver tissue from a dog to which carbon tetrachloride was administered.

Grossly the liver was enlarged, hard and granular and had many gray and red patches. The approximate weights of the livers were 285, 250 and 286 Gm. respectively. The weights at autopsy were 493, 512 and 490 Gm.

Microscopically the liver cells showed disintegration and complete areas of atrophy, with considerable extravasation of blood cells and massive hemorrhage. Some areas were observed with fat vacuolation and central necrosis. The Kupffer cells showed a dark nucleus.

Figures 7 and 8 are reproductions of photomicrographs of liver tissue as described.

Physical Condition of Dogs: Our animals were in good condition throughout the experiments, and each procedure was carried out under standard environment.

TABLE 3.—*Schedule of Dogs Given Carbon Tetrachloride*

Dog	Date	Weight, Pounds	Duration of Experiment, Months	Weekly Dose, Cc.	Condition of Dog 24 Hours Before Death	Liver	
						Biopsy	Autopsy
5	2/ 9/38	20	13	60	Good	Fibrosis	Fibrotic; nodular; enlarged
7	3/22/38	23	33	60	Good	Fibrosis	
24	4/18/40	24	8	60	Good	Fibrosis	

TABLE 4.—*Values for Gastric Acidity (Dogs 5, 7 and 24)*

Dog	Values Before Experiment, mEq.		Experimental Stage, Mo.	Maximul Values for Acid, mEq.		Experimental Stage, Mo.	Maximal Values for Acid, mEq.		Experimental Stage, Mo.	Maximal Values for Acid, mEq.	
	Free	Total		Free	Total		Free	Total		Free	Total
5	138.0	163.6	9	48.0	72.0	13	65.2	117.2	..	Mortality	
7	129.6	155.2	8	64.0	92.0	13	120.0	142.0	28	50.0	100.0
24	110.0	161.0	5	66.0	100.0	8	102.0	145.0	..	In progress	

Figure 9 shows 1 of our animals. The denuded areas on the extremity are areas at which radiation was applied. This particular dog was used as a control. Direct irradiation of the liver was subsequent to irradiation of the extremity.

Carbon Tetrachloride.—The data on dogs given carbon tetrachloride are presented in table 3.

Gastric Acidity: In dogs 5, 7 and 24 a decrease was noted in the values for free and total acidity in the early stages of the experiment; this was followed by a recovery of the gastric acidity curve to a level near normal. In the terminal stages of the experiment the values for acidity were again decreased. The values for dogs 5, 7 and 24 are shown in table 4.

In figure 10 we demonstrate the behavior of the gastric acidity following administration of carbon tetrachloride, showing the "initial decrease," the period of recovery and the "final decrease" of the terminal stage of the experiment.

Liver: Grossly the liver was large, hard, nodular, fibrotic and brownish gray. The approximate weight of the livers of dogs 5, 7 and 24 was 320, 255 and 280 Gm. respectively. The weight at autopsy of the liver of dog 5 was 455 Gm.

Microscopically there was evidence of cellular infiltration, atrophy of cells and fatty changes. The fibrous tissue deposits were enormous and caused distortion of the liver lobules.

Figures 11 and 12 demonstrate the pathologic changes in the liver.

Figure 13 is a photograph of dog 7, which has been given carbon tetrachloride for thirty-three months. The animal is in very good condition. It weighs 4 pounds (1.8 Kg.) less than it weighed originally.

Fig. 13.—Dog 7. This animal was given carbon tetrachloride for thirty-three months.

COMMENT

Duggar [3] stated that after irradiation of human subjects "chronic changes in the livers are rarely observed because either the subject succumbs to massive destruction from large doses, or the regeneration after smaller doses is so rapid and complete as to leave little or no residual. There is considerable evidence of rapid recovery of the liver function. But if sufficient radiation is given repeatedly in proper sequence and dosage, extensive irreparable damage might be obtained. A comprehensive, well correlated study of the effects of roentgen rays on the liver is needed."

3. Duggar, B. M.: Biological Effects of Radiation, New York, McGraw-Hill Book Company, Inc., 1936, vol. 1.

Many authors have stated that no histologic change in the liver is evident after irradiation, while others have reported injuries of all types. Pohle and Bunting [4] described swelling and atrophy of the cells. Doub [5] reported the liver as reduced in weight and showing extensive fatty infiltration, some increase in fibrous tissue and a loss of orderly cell arrangement.

In irradiated animals the livers were increased in weight and showed atrophy and disintegration; in animals given carbon tetrachloride the livers were enlarged and nodular and displayed more evidence of fibrous tissue deposits.

In the experiments with radiation applied directly against the stomach the pathologic changes involved chiefly the secretory epithelium. Dawson [6] observed that the chief cells are the most sensitive, while the parietal cells are resistant. The decrease in acidity of the gastric juice is one of the characteristic reactions to irradiation, according to Dawson [6] and Portis and Ahrens,[7] and should be attributed to cell injury. The stomachs of our animals showed microscopic evidence of degeneration and we therefore are inclined to attribute alterations in secretory mechanism to injury of the cells of the stomach. On the basis of the findings of Dawson one may assume that the toxic elements produced by irradiation of the liver act secondarily to produce changes in the stomach such as are produced by irradiation of the stomach. The results presented show that changes in gastric acidity are produced when the liver is damaged either by direct irradiation or by intragastric administration of carbon tetrachloride.

With direct irradiation of the liver there is first an initial rise in the gastric acidity; this is followed by a decrease and a subsequent return to the pretreatment level provided no further radiation is administered. The gradual return to a pretreatment level of the gastric acidity is probably the result of regeneration of the damaged liver or a compensatory response in the form of increased activity by the uninjured portion of the liver. Repeated irradiation depresses the free and total acidity more and more with each treatment. In other words, the degree

4. Pohle, E. A., and Bunting, C. H.: Studies of the Effect of Roentgen Rays on the Liver: Histological Changes in the Liver of Rats Following Exposure to Single Graded Doses of Filtrated Roentgen Rays, Acta radiol. **13**:117, 1932.

5. Doub, H. P.; Bolliger, A., and Hartman, F. W.: Immediate Metabolic Disturbance Following Deep Roentgen Ray Therapy, Am. J. Roentgenol. **13**:54, 1925.

6. Dawson, A. B.: Histological Changes in the Gastric Mucosa (Pavlov Pouch) of the Dog Following Irradiation, Am. J. Roentgenol. **13**:320, 1925.

7. Portis, S. A., and Ahrens, R.: The Effects of the Shorter Wave Length Roentgen Ray on the Gastric Secretion of Dogs, Am. J. Roentgenol. **11**:272, 1924.

of gastric secretory disturbance is in proportion to the amount of hepatic damage and the relative amount of toxic absorption. The limit of the disturbance of the gastric secretory mechanism is also gaged by the amount of damage the liver can withstand.

When the damage to the liver is irreparable, the dog does not recover and the values for acidity fall progressively.

Our impression is that the initial rise in acidity is brought about probably by liberation of a histamine-like substance when the liver is damaged by irradiation; the gradual decrease follows because of a disturbance in the secretory mechanism produced secondarily, in the form of gastritis due to toxic absorption. This disturbance is not permanent; the damage to the liver is apparently reparable, as the acidity curve rises to the original level. Ivy, McCarthy and Orndoff [8] stated that in all probability the initial and transient increase in gastric secretion is to be regarded as an effort on the part of the secreting cells to counteract the noxious influence of the rays; this effort appears during the early phase of reaction, to disappear later and be replaced by secretory depression. It is of interest to note that irradiation of the muscles of the extremity did not bring about any changes in the gastric acidity; this leads to the conclusion that some specific factor is elaborated by direct irradiation of the liver which is responsible for the alterations in gastric secretion.

The gastric juices in these experiments were apparently highly buffered, and the chemical constituents which may be responsible for the buffered activity were recognizable at hydrogen ion concentrations between 3 and 5 and between 6 and 7. These constituents are probably proteins.

The results obtained with carbon tetrachloride were different from those obtained with irradiation. There was no evidence of stimulation. Varying degrees of depression were noted. In these experiments there was first an initial decrease in the free and total acidity and later a return of the acidity to the original level. The initial disturbance was apparently parallel to the amount of toxic absorption and was transient, as continued administration of carbon tetrachloride did not prevent the acidity curve from returning to a level near normal. However, further administration of the drug eventually brought about a secondary depression in the secretory mechanism which was more exaggerated and more prolonged than the initial depression.

---

8. Ivy, A. C.; McCarthy, J. E., and Orndoff, B. H.: Studies on the Effects of Roentgen Rays on Glandular Activity: Effect of Exposure of Abdominal and Thoracic Areas to Roentgen Rays on Gastric Secretions; Roentgen Cachexia, J. A. M. A. **83**:1977 (Dec. 20) 1924.

CONCLUSIONS

There is evidence that a disturbance occurs in the acid-secretory mechanism of the stomach secondary to moderate or severe damage to the liver.

Progressive damage to the liver depresses the acidity of the gastric juice.

In these experiments the gastric juice obtained from the Pavlov pouch was apparently highly buffered.

The buffered action of the gastric juice obtained was apparently due to chemical constituents (perhaps proteins) which are recognizable at hydrogen ion concentrations between 3 and 5 and between 6 and 7.

Marked microscopic changes were noted in the livers of dogs exposed to radiation and in dogs to which carbon tetrachloride had been administered.

Degenerative changes were noted in the cellular elements of the gastric mucosa.

Dr. Robert W. Keeton, head of the department of medicine of the University of Illinois, made helpful suggestions for this work. Mr. Solomon Bishov and Mr. Robert Long contributed technical assistance.

BASAL CELL EPITHELIOMA OF THE ANUS

REPORT OF TWO CASES

KNOWLES B. LAWRENCE, M.D.
BOSTON

The rarity of basal cell epithelioma of the anus was demonstrated by Guess [1] in 1935. He found no tumors of this type listed in the records of 150,000 biopsies at the State Institute for Malignant Disease at Buffalo. There was no mention of this tumor in a group of reports on 2,000 anal and rectal malignant tumors which he collected from the literature. Guess reported 1 personally observed case of anal basal cell carcinoma. The tumor was a small lesion. Four local excisions of supposed external hemorrhoids and tabs had been done prior to histologic examination of the tissue. This tumor was treated with 1,400 millicurie hours of interstitial radiation in the form of gold radon seeds. Healing occurred in ten weeks. The patient died of coronary thrombosis five years later, without evidence of recurrence of the tumor.[2]

In a review from the Mayo Clinic (1933) Buie and Brust [3] listed only 51 cases of malignant anal lesions of epithelial origin. These represented 1.73 per cent of the total 2,939 cases of anorectal malignant tumors studied. Two of the 51 patients had basal cell lesions. In 1 of these the lesion was annular and fairly bulky. Colostomy, posterior resection of the rectum and anus and implantation of radium were tried, but there was a local recurrence of the growth eight months after the operation and the patient died of the disease one month later. The second patient had a tumor the size of an orange at the anal margin. Radium treatment was refused, and the patient could not be followed. Enlarged nodes were present in the inguinal regions in both cases. In a recent personal communication Buie [4] expressed the belief that these nodes did not contain metastatic malignant growth. Tucker and Helwig [5]

From the Pondville Hospital at Norfolk, Wrentham (Massachusetts Department of Public Health).

1. Guess, H. C.: Basal Cell Epithelioma of the Anus, Tr. Am. Proct. Soc. **36**:81-84, 1935.

2. Guess, H. C.: Personal communication to the author.

3. Buie, L. A., and Brust, J. C. M.: Malignant Anal Lesions of Epithelial Origin, Journal-Lancet **53**:565-571 (Nov.) 1933.

4. Buie, L. A.: Personal communication to the author.

5. Tucker, C. C., and Helwig, C. A.: Proctologic Tumors, J. A. M. A. **111**: 1270-1273 (Oct. 1) 1938.

reported a single case of basal cell epithelioma of the anus. The tumor was a very small lesion represented by a nearby microscopic focus of neoplastic tissue about a hair follicle in a tab of tissue removed at hemorrhoidectomy. The patient was treated with high voltage roentgen therapy with a total of 3,414 roentgens, after which 50 mg. of radium was placed in the anal canal for 600 milligram hours of radiation. No recurrence was observed at the most recent examination, November 1940 (three years after the operation).[6]

The 2 cases of basal cell epithelioma of the anus reported here are the only cases to be found in the records of the Pondville Hospital, Wrentham, Mass., an institution for persons with cancer, where 17,462 patients have been treated in thirteen years. In the same period, carcinoma of the anus or rectum was present in 635 cases. Of this group, 21 (3.3 per cent) were classified as instances of primary anal carcinoma. These were further grouped pathologically as follows: epidermoid carcinoma, 15 cases; adenocarcinoma, 4 cases, and basal cell carcinoma, 2 cases. In 3 instances the adenocarcinoma was sufficiently bulky to make differentiation from primary rectal carcinoma difficult.

REPORT OF CASES

CASE 1.—A 73 year old French Canadian woman was admitted to the Pondville Hospital Dec. 10, 1939, complaining of a growth about the anus of one year's duration. This growth was external and had gradually increased in size. There had been a constant serous discharge and minor amounts of bleeding from irritation of clothing frequently during recent months. The patient had no other serious complaints and was in reasonably good health for her age. No history of previous anal symptoms or of operation could be elicited.

The patient was fairly well preserved. She appeared slightly anemic. The blood pressure was 200 systolic and 100 diastolic, but the heart was only slightly enlarged. Several rather firm but movable lymph nodes could be felt in either inguinal region; they varied up to 1.5 cm. in diameter, the larger nodes being on the left side. An annular fungating growth completely involved the anus, extending at least 2 cm. into the adjacent perineum and perianal tissues and upward to just above the level of the internal sphincter. The growth was firm. It narrowed the anal orifice considerably but was moderately movable en masse. There was superficial ulceration in places, and mild secondary infection was noted. The remainder of the physical examination gave essentially negative results.

Laboratory studies revealed moderate secondary anemia, with 3,450,000 erythrocytes per cubic millimeter of blood and 55 per cent hemoglobin (Sahli). The other data were not remarkable. A biopsy of the tumor was performed, and the diagnosis was basal cell carcinoma. Roentgenograms of the skull, spine and pelvis revealed no metastatic disease of bone.

On December 19, after preliminary cleansing of the colon, a permanent loop colostomy was performed with the area under local procaine hydrochloride anesthesia. Abdominal exploration showed no metastatic disease, and the lesion was judged locally resectable. The age and the generally diminished vigor of the patient made radical abdominoperineal resection seem unwise.

6. Tucker, C. C.: Personal communication to the author.

The patient did well after the colostomy, although she was bothered considerably by an infection of the bladder. As secondary infection in the growth subsided, the inguinal nodes became barely palpable. Posterior resection of the rectum with an adequate margin of skin and tissue about the growth was per-

Fig. 1 (case 1).—Basal cell epithelioma of the anus in situ.

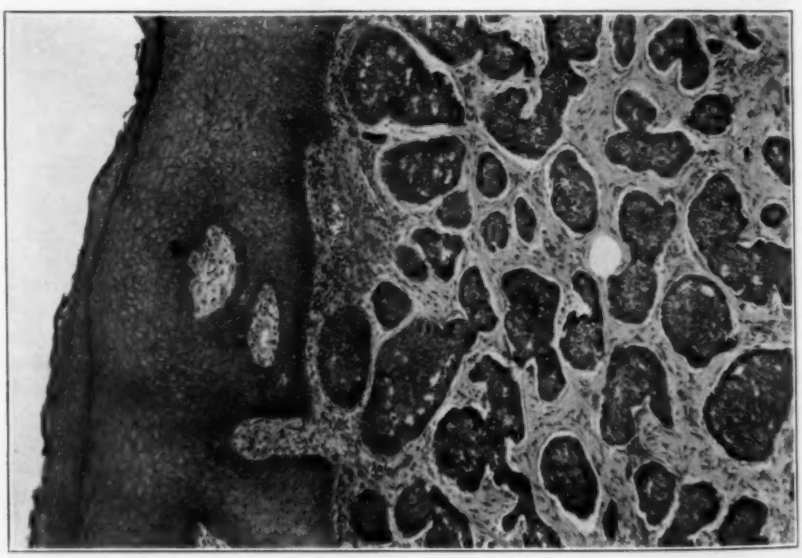


Fig. 2 (case 1).—Photomicrograph of a section of a basal cell epithelioma of the anus.

formed on Jan. 15, 1940. Because of a small accidental perforation of the rectum during the removal, two doses of gas bacillus antiserum (5,000 units each) were administered postoperatively. On the morning of the second day smears of material from the gauze drain showed organisms resembling Bacillus welchii. This was confirmed on culture. There was, however, no clinical

appearance of gas bacillus infection. Auricular fibrillation then developed but was controlled by digitalis. Within a few days the patient became psychotic; she was noisy, restless and at times irrational. The posterior wound began to heal satisfactorily. On February 4 and 8 the patient had generalized convulsive seizures, and then declined rapidly; coma and terminal bronchopneumonia developed, and death occurred three days later.

Permission for autopsy could not be obtained. The description of the operative specimen (Dr. Shields Warren) was as follows:

The specimen consisted of an excised anus with 5 cm. of rectum attached. The anus was transformed into an irregularly outlined crateriform lesion measuring about 7 cm. in its greatest diameter, with many firm marginal tags varying greatly in size and covered with pearly white thickened epithelium. The floor of the ulcer was slightly nodular and clean, with induration of the underlying tissues. The rectal mucosa proximal to the lesion appeared entirely normal (fig. 1). Microscopically, bizarre ramifying masses of crowded polyhedral to ovoid cells were seen beneath the normal or only slightly proliferating epithelium. The nuclei were ovoid and hyperchromatic. There was moderate mitotic activity, and in rare foci keratinization of the cells was noted. The surrounding stroma was patchily infiltrated with plasma cells and lymphocytes. Some areas of the tumor showed necrosis, with a heavy polymorphonuclear leukocytic infiltration (fig. 2). The diagnosis was basal cell carcinoma.

CASE 2.—A 68 year old white man, a retired shoemaker, was admitted to the Pondville Hospital July 2, 1937, because of rectal discomfort of eleven months' duration. At the onset he had noted a mass protruding from the anus, which he interpreted as "piles." There was no bleeding. A physician was first consulted four months prior to his admission to Pondville, because of increase in the anal pain (after defection) and slight diarrhea. Rectal examination was not made, though a salve was prescribed. Later great tenesmus and rectal incontinence developed, together with an increase in other symptoms. No complaints referable to the urinary tract were noted. The patient stated that he had had no previous anal trouble.

The positive physical abnormalities were limited to the anal area, which was the site of a hard, nearly annular fungating neoplasm. It measured 6 cm. in its greatest surface diameter. The growth involved the sphincter and caused considerable stenosis of the anal canal, permitting only limited digital examination. The lesion seemed attached to the prostate. A number of movable, slightly enlarged lymph nodes could be felt in both external inguinal and femoral regions. There was no abdominal distention or masses.

Laboratory studies revealed moderate secondary anemia. The erythrocyte count was 3,610,000 per cubic millimeter of blood, and the value for hemoglobin (Sahli) was 72 per cent. The other data were irrelevant. On biopsy the anal lesion was diagnosed as basel cell carcinoma.

A loop colostomy was performed on July 12, followed eight days later by posterior excision of the anus and rectum. Anteriorly the neoplasm was found to invade the prostate and the membranous urethra. In leaving the latter structure intact it was necessary to cut through what appeared to be tumor tissue. The postoperative course was satisfactory, and the wound of the posterior resection healed well, without gross evidence of recurrence of the tumor. It was decided to reserve roentgen treatment until recurrence developed. The follow-up was by

letter, since the patient lived at a distance. He was fairly well for nearly two years (without further treatment); then he gradually became ill, and he died at home April 2, 1940. Autopsy was not performed.

Pathologic examination of the resected tumor revealed a picture generally similar to that of the specimen in case 1. In case 2 there was a somewhat greater tendency of the tumor to invade the surrounding tissues; it involved even the rectal mucosal glands. The microscopic diagnosis was basal cell carcinoma.

COMMENT

Because of the extent of the lesion in each patient it was impossible to ascertain definitely from what portions of the anal canal it arose.

There was no prior history of hemorrhoids or of any other chronic rectal disease. Several authors have felt that preexisting chronic, nonmalignant anal conditions, such as hemorrhoids, anal skin tabs, fissures and fistulas, are precursors of anal malignant tumor in a large percentage of cases.[7] Because of this real danger, routine microscopic examination should be done on all tissues removed at anal operations, even though they show clinically no sign of malignant growth. The basal cell carcinomas described by Guess [1] and by Tucker and Helwig [5] were discovered because of such routine studies. The latter authors found by routine microscopic examination 1.9 per cent of unsuspected malignant tumors in tissues from 951 anorectal operations for benign conditions.

Histologically the tumors described here presented the usual features of basal cell epithelioma. Relatively numerous mitotic figures and the rare foci of keratinized cells present in both specimens were somewhat atypical but favored more rapid growth and may have accounted for the bulk and extent of the tumors. Spontaneous regression of the inguinal and femoral lymphadenopathy after diversion of the fecal stream in the first case suggests that this was inflammatory. Basal cell epithelioma in other regions of the body rarely if ever metastasizes to lymph nodes. I am therefore skeptical of its occurrence in basal cell lesions involving the anus.

The question of the type of treatment is important. In 2 of the cases from the literature [8] the patients have remained free of disease five and three years respectively after local excision and radium treatment in 1 case and after local excision followed by radium and roentgen irradiation in the other. The lesions were small and probably would have done equally well with operation alone if sufficiently radical. The larger of the 2 lesions described in the cases reported by Buie and Brust [3] recurred fatally eight months after a combination of posterior resection of the anorectal region and implantation of radium. The patient in their other case refused any treatment.

---

7. Rosser, C.: Etiology of Anal Carcinoma, Am. J. Surg. **11**:328-333 (Feb.) 1931. Guess.[1] Tucker and Helwig.[5]

8. Guess.[1] Tucker and Helwig.[5]

The operative death of 1 of the patients described in this report eliminated the possibility of what might have been good palliation or even cure following posterior resection for a bulky anal lesion. In the other patient there was involvement of the membranous urethra and prostate, and it was not possible to remove all of the gross tumor. That the patient lived two years longer is testimony to the slow growth of the lesion. Postoperative roentgen treatment in this case might have provided additional palliation.

A bulky basal cell epithelioma will probably react most favorably to colostomy and posterior resection of the anorectum in the patient who is a satisfactory operative risk. A wide margin of normal tissue should be removed with the tumor. Because this lesion seems uninclined to metastasize to the regional nodes, there is small argument for a radical abdominoperineal resection, which is obviously advisable for epidermoid carcinoma of the same region. Should the biopsy reveal some tendency in the tumor toward squamous cell metaplasia or show a mixed basal cell–squamous cell structure, resection of the regional nodes would seem indicated. Radium and roentgen therapy should prove satisfactory for a small basal cell lesion if given in fairly large doses and should also afford considerable palliation of a bulky lesion in a patient who is a poor operative risk.

SUMMARY

Two cases of basal cell epithelioma of the anus are reported. In a review of the literature the extreme rarity of this tumor is stressed, only 4 cases having been listed previously.

The favored mode of treatment has been posterior resection of the anorectum, with or without postoperative irradiation, for the bulky lesions and radium therapy and irradiation for the smaller tumors.

Because of the few reported instances of this lesion, no statement regarding the prognosis is possible.

FUNCTIONAL EFFECT OF NEO-SYNEPHRIN ON THE ANESTHETIZED DOG

OBSERVATIONS OF BLOOD PRESSURE, PULSE, RESPIRATION AND FLOW OF URINE AND BILE

PAUL H. LORHAN, M.D.
AND
J. G. SCHNEDORF, M.D., PH.D.
KANSAS CITY, KAN.

Since Tainter and Stockton's [1] original report on the effectiveness of neo-synephrin as a systemic vasoconstrictor stimulant, its use as a vasopressor drug for spinal anesthesia has been reported by numerous investigators.[2] These workers have reported its effect in elevating and sustaining the blood pressure during spinal anesthesia. The associated bradycardia has also been discussed thoroughly.

The action of neo-synephrin on the respiration has been briefly commented on by Tainter and Throndson [3] and by Tainter, Throndson and Moose [4] in conjunction with its use in solutions of procaine hydrochloride

---

From the Hixon Laboratory for Medical Research, the University of Kansas.

1. Tainter, M. L., and Stockton, A. B.: Comparative Action of Sympathicomimetic Compounds: The Circulatory and Local Actions of the Optical Isomers of Metasynephrin and Possible Therapeutic Applications, Am. J. M. Sc. **185**:832, 1933.

2. (*a*) Johnson, C. A.: A Study of Neo-Synephrin Hydrochloride in the Treatment of Acute Shock from Trauma or Hemorrhage, Surg., Gynec. & Obst. **63**:35, 1936. (*b*) Johnson, C. A.: Neo-Synephrin Hydrochloride in the Treatment of Hypotension and Shock from Trauma or Hemorrhage, ibid. **65**:458, 1937. (*c*) Lorhan, P. H., and Olivero, R. M.: A Study of the Use of Neosynephrin Hydrochloride in Spinal Anesthesia, Anesth. & Analg. **17**:44, 1938. (*d*) Bittrick, N. M.: Clinical Use of Neosynephrin Hydrochloride for Control of Blood Pressure During Spinal Anesthesia, ibid. **18**:29, 1939. (*e*) Brunner, R. S., and de Takáts, G.: Use of Neosynephrine in Spinal Anesthesia, Surg., Gynec. & Obst. **68**:1021, 1939. (*f*) Lorhan, P. H., and Lalich, J.: Circulatory and Electrocardiographic Studies of Neosynephrin Hydrochloride in Spinal Anesthesia, Anesth. & Analg. **19**:66, 1940. (*g*) Silvers, H. I., and Leonard, I. E.: The Use of Neosynephrin Hydrochloride in Maintaining Blood Pressure During Spinal Anesthesia, Am. J. Surg. **50**:79, 1940.

3. Tainter, M. L., and Throndson, A. H.: Influence of Vasoconstrictors on the Toxicity of Procaine Anesthetic Solutions, J. Am. Dent. A. **25**:966, 1938.

4. Tainter, M. L.; Throndson, A. H., and Moose, S. M.: Influence of Vasoconstrictors on the Clinical Effectiveness and Toxicity of Procaine Anesthesia Solution, J. Am. Dent. A. **25**:1321, 1938.

as a local anesthetic for dental nerve blocking. Their results indicated that the action of neo-synephrin on the respiration is not of great clinical significance.

Data relative to the effects of neo-synephrin on urinary excretion are meager. Boyd [5] reported that 0.5 cc. of a 0.01 per cent solution of neo-synephrin hydrochloride caused a marked antidiuretic action analogous to that of epinephrine. Zunz and Sparchez [6] found that 0.4 to 0.8 mg. of neo-synephrin hydrochloride administered intravenously to dogs resulted in an increase in the output of urine and that 1.6 to 3.2 mg. diminished or abolished the output of urine.

PURPOSE OF PRESENT STUDY

This investigation was undertaken to determine the pharmacologic action of neo-synephrin on the blood pressure, pulse, respirations and flow of urine and bile in the dog.

METHOD

Six fasting dogs under pentobarbital sodium anesthesia were used in the first part of this experiment. The blood pressure was recorded from the cannulated left carotid artery. Kymographic tracings of the depth and rate of respiration were obtained by means of a bellows around the chest and the upper part of the abdomen. Both ureters were cannulated, and the flow of urine was recorded by means of an electrical recorder. The common bile duct was cannulated in 4 dogs, and the bile flow was recorded by an electrical recorder.

The effects of the intravenous administration of 2 minims (0.12 cc.; 1.24 mg.), 4 minims (0.25 cc.; 2.48 mg.) and 10 minims (0.65 cc.; 6.2 mg.) of a 1 per cent solution of neo-synephrin hydrochloride on the blood pressure, pulse, respiration and flow of urine and bile were then determined.

The action of neo-synephrin on the blood pressure, pulse, respiration and urine flow in the presence of peripheral vascular failure was also studied in 5 dogs. Shock was produced by the slow intravenous administration of histamine in physiologic solution of sodium chloride at such a rate that the blood pressure was maintained between 18 and 40 mm. of mercury.

RESULTS

Intravenous injection of 2, 4 and 10 minims of a 1 per cent solution of neo-synephrin hydrochloride into normal dogs and into dogs under histamine shock produced changes in blood pressure similar to the results obtained by Tainter and Stockton [1] and by Johnson [2a] and hence need not be discussed further. Marked slowing of the pulse occurred in the normal animals and in those with histamine shock. In the normal dogs

5. Boyd, E. M.: The Pharmacology of Meta-Synephrin, J. Pharmacol. & Exper. Therap. **60**:174, 1937.

6. Zunz, E., and Sparchez, T.: Effects des Oxyphénylméthylaminoéthanols sur la diurèse aqueuse, Compt. rend. Soc. de biol. **124**:1257, 1937.

2 minims of neo-synephrin hydrochloride solution slowed the average pulse rate from 162 to 76; 4 minims slowed the pulse rate to an average of 58, and after a dose of 10 minims the average pulse rate was 75. In the animals with histamine shock the pulse rate decreased from an average of 180 to 126 after injection of 2 minims of neo-synephrin hydrochloride solution. After injection of 4 minims the rate slowed to 50, and after injection of 10 minims the average rate was 80.

TABLE 1.—*Effect of Neo-Synephrin on the Blood Pressure, Pulse, Respiration and Flow of Urine and Bile in the Anesthetized* Normal Dog*

Dog	Dose, Minims †	Blood Pressure	Pulse Rate	Respiration		Apnea	Flow of Urine, Cc. per Hour	Flow of Bile, Cc. per Hour
				Depth	Rate			
1	..	160	220	—	164	..	21.6	....
	2	180	100	+	40	—	31.2 (+44%)	
	4	240	60	—	92	+ 25 seconds	9.0 (−58%)	
	10	280	60	—	120	+ 90 seconds	Anuria 75 min. (−100)	
2	..	100	160	+	15	..	36.0	....
	2	200	120	+	12	+ 10 seconds	39.0 (+8.3%)	
	4	240	96	+	9	+ 30 seconds	5.1 (−85%)	
	10	220	108	—	8	+	1.4 (−96%)	
3	..	110	160	+	68	..	60.0	12.0
	2	220	92	—	28	—	26.4 (−56%)	9.6 (−20%)
	4	236	40	—	40	—	1.2 (−98%)	12.0 (0)
	10	220	60	—	8	—	3.0 (−95%)	6.0 (−50%)
4	..	110	100	—	36	..	75.0	10.5
	2	180	40	+	12	+ 60 seconds	30.0 (−61%)	6.0 (−42%)
	4	240	70	+	12	+ 45 seconds	6.0 (−92%)	3.6 (−65%)
	10	240	88	—	12	—	5.4 (−92.7%)	3.0 (−71%)
5	..	90	200	—	30	..	135.0	15.0
	2	180	60	—	18	—	36.0 (−73%)	9.0 (−40%)
	4	200	52	+	23	—	13.8 (−89%)	6.0 (−60%)
	10	200	80	+	20	—	8.4 (−93%)	7.8 (−48%)
6	..	100	136	—	40	..	36.0	15.0
	2	140	42	0	32	—	30.0 (−16%)	10.2 (−32%)
	4	180	20	+	12	+ 80 seconds	6.0 (−83%)	1.8 (−88%)
	10	170	60	—	48	—	5.0 (−86%)	0.6 (−96%)

* Pentobarbital sodium was used.
† Of a 1 per cent solution of neo-synephrin hydrochloride.

With the increase in blood pressure and slowing of the pulse there also occurred an increase in the pulse pressure. Cardiac irregularities were noted in the normal animals and in those with histamine shock following the intravenous administration of 10 minims of neo-synephrin hydrochloride solution.

The respirations were markedly affected by neo-synephrin for the first five to ten minutes, after which they returned to normal. Of the

normal dogs, the depth of respiration was increased in 3 after injection of 2 minims of neo-synephrin hydrochloride solution; it was decreased in 2, and there was no change in 1. After injection of 4 minims the depth increased in 4 dogs and decreased in 2. The depth of respiration decreased markedly in 5 dogs after a dose of 10 minims; 1 animal showed an increase in depth of respiration. Of the dogs in histamine shock the depth of respiration was decreased in all except the animal which received 10 minims.

The average respiratory rate of 69 in the normal dogs decreased to 14 after administration of 2 minims of neo-synephrin hydrochloride solution intravenously. After administration of 4 and 10 minims the rate averaged 31 and 36 per minute respectively. Two minims of neo-

TABLE 2.—*Effect of Neo-Synephrin on Anesthetized* Dogs in Histamine Shock*

Dog	Dose, Minims †	Blood Pressure	Pulse Rate	Respiration		Apnea	Flow of Urine, Cc. per Hour
				Depth	Rate		
1	..	18	152	—	60	..	...
	10	120	80	+	48	+ 90 seconds	...
2	..	40	180+	—	16	..	...
	2	60	120	—	15	+ 30 seconds	...
3	..	30	180	—	46	..	...
	2	120	120	—	16	+ 70 seconds	...
4	..	30	180	—	30	..	12
	2	120	140	—	60	+ 60 seconds	1.2 (—90%)
6	..	40	180	—	19	..	19.2
	4	160	50	—	14	+ 30 seconds	1.6 (—91%)

* Pentobarbital sodium was used.
† Of a 1 per cent solution of neo-synephrin hydrochloride.

synephrin did not significantly affect the respiration of the dogs in histamine shock; however, 4 and 10 minim doses produced a slight decrease in the rate.

In the normal animals, coincidental with the slowing of the respiration, periods of apnea occurred which varied from ten to ninety seconds in duration. In the animals with histamine shock the period of apnea varied from thirty to ninety seconds.

The excretion of urine decreased 16 to 73 per cent below normal after administration of 2 minims of neo-synephrin hydrochloride solution in 4 dogs and increased 8.3 and 44 per cent above normal in 2 dogs. After administration of 4 minims the urinary excretion decreased 58 to 98 per cent in all 6 dogs. After injection of 10 minims the excretion of urine decreased 86 to 100 per cent below normal. One animal had complete anuria for one hour and fifteen minutes. Two minim and

4 minim doses caused a decrease in the urine flow of 90 and 91 per cent below normal in 2 dogs in histamine shock.

Neo-synephrin caused a decrease in the rate of bile flow in all 4 dogs. With 2 minims of neo-synephrin hydrochloride solution the bile flow decreased 20 to 42 per cent below normal. The administration of 4 minims caused a decrease of 60 to 88 per cent in 3 animals, and 1 dog showed no change. After a dose of 10 minims the bile flow decreased 48 to 96 per cent below the normal control flow.

COMMENT

The effect of neo-synephrin on the circulation has been discussed by Tainter and Stockton.[1] However, it may be said that in addition to the slowing of the pulse there occurs an increase in the pulse pressure.

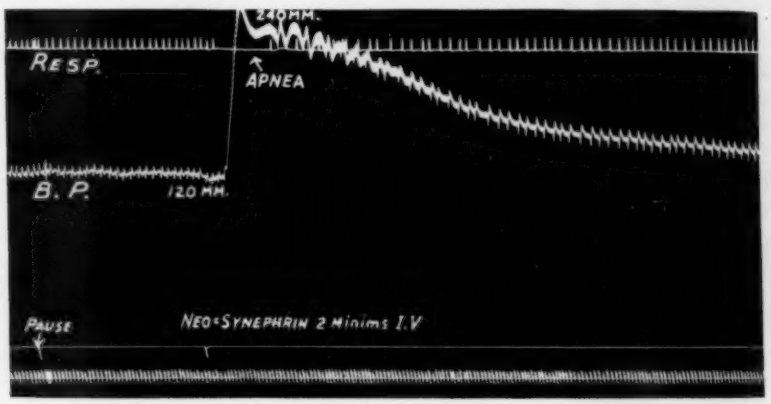


Chart 1 (dog 2).—Apnea, slowing of respiration and sharp rise in blood pressure in the dog following intravenous injection of 2 minims (0.12 cc.) of a 1 per cent solution of neo-synephrin hydrochloride (1.24 mg.).

With the associated bradycardia the ventricles are allowed to fill more fully during the prolonged period of diastole, so that with the systolic contraction of the heart the stroke output is increased. Keys and Violante [7] have demonstrated that the left side of the heart shows the most pronounced increase in size, but to them all parts of the heart appear to share in the dilatation, and the original form of the heart is well preserved in both systole and diastole. After the administration of 10 minims of a 1 per cent solution of neo-synephrin hydrochloride cardiac irregularities are noted, especially dropped beats and extrasystoles. In this respect neo-synephrin is similar to epinephrine when it is given in large doses. The intravenous administration of 10 minims

7. Keys, A., and Violante, A.: Size and Stroke of the Normal Human Heart During Neosynephrin Bradycardia, Proc. Soc. Exper. Biol. & Med. **44**:462, 1940.

of neo-synephrin hydrochloride solution is not considered good clinical practice, because of the cardiac effects of the drug.

The intravenous administration of neo-synephrin will produce apnea lasting ten to ninety seconds in the normal animal and thirty to ninety seconds in dogs in histamine shock. This "neo-synephrin apnea" develops at the time of the rise in blood pressure and within the first five minutes after injection of the neo-synephrin. In this respect neo-synephrin is similar to epinephrine. Epinephrine lacks the property of stimulating the respiratory center and consequently has no appreciable direct effect on the respiratory rate. The "epinephrine apnea" is, however, produced indirectly through a reflex inhibition caused by the increased pressure in the carotid sinus and in the cardioaortic areas.[8] McDowall[9] stated the opinion that the slowed respiration and bradycardia following the injection of epinephrine are caused by the same

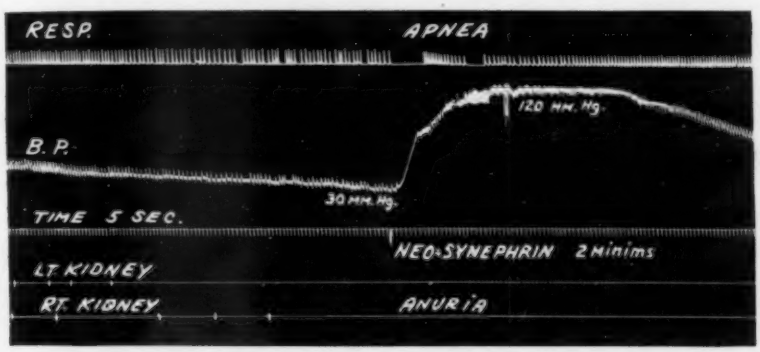


Chart 2 (dog 5).—Transient apnea and anuria following rise in blood pressure of a dog in histamine shock on intravenous injection of 2 minims of a 1 per cent solution of neo-synephrin hydrochloride (1.24 mg.).

inhibitory vagus reflex. The "neo-synephrin apnea" observed in our dogs was probably due to the same reflex action on the carotid sinus and the cardioaortic areas as a result of the increased blood pressure following its injection.

Neo-synephrin is different from ephedrine. The latter influences respiration in two ways: first, by a direct stimulation of the respiratory center, and, second, by dilating the bronchioles through a peripheral sympathomimetic action similar to that of epinephrine.[10] Tainter, Pedden

8. Heymans, C., and Bouckaert, J. J.: Sinus Caroticus and Respiratory Reflexes: Cerebral Blood Flow and Respiration, Adrenaline Apnoea, J. Physiol. **69**:254, 1930.

9. McDowall, R. J. S.: Effects of Adrenaline on Respiration, Quart. J. Exper. Physiol. **18**:325, 1928.

10. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, p. 428.

and James,[11] in studying the bronchodilating properties of various sympathomimetic compounds, found that neo-synephrin caused good bronchiolar dilation, but not as much as epinephrine.

The generalized peripheral vasoconstriction that neo-synephrin produces likewise affects the renal and hepatic vessels, causing constriction of the vessels themselves and thereby decreasing and diminishing the flow of blood to the kidneys and the liver. Zunz and Sparchez [6] observed a slight increase in urinary flow after small doses but a decrease after large doses. The results obtained here show that 2 minim doses of a 1 per cent solution of neo-synephrin hydrochloride have a slight variable effect on the excretion of urine. Four and 10 minim doses, however, cause a marked decrease in the flow of urine, and in some instances anuria develops, which may persist for an hour or more. Massive doses, therefore, are not to be used, because of the anuria and decrease of urinary flow that may occur.

The bile flow is likewise diminished an average of 33 per cent after administration of 2 minims of neo-synephrin hydrochloride solution. This may be due to constriction of the hepatic arterioles. After administration of 4 minims the bile flow was decreased on an average of 71 per cent in 3 dogs, with no change in 1. The administration of 10 minims resulted in an average 66 per cent decrease in bile flow in the 4 dogs studied.

SUMMARY

The effect of neo-synephrin hydrochloride on the blood pressure, pulse, respiration and flow of urine and bile in 6 normal dogs anesthetized with pentobarbital sodium was studied. Its effect on 5 dogs in histamine shock was also studied.

Neo-synephrin produced a marked rise in the blood pressure associated with bradycardia and an increase in the pulse pressure. The intravenous injection of 10 minims of neo-synephrin hydrochloride caused cardiac irregularities.

The effect of neo-synephrin on the respiration occurred in the first five to ten minutes after its injection. There was a decrease in the depth and rate of respiration. In some instances apnea lasting ten to ninety seconds was observed.

Two minims of a 1 per cent solution of neo-synephrin hydrochloride produced a mild variable effect on the flow of urine and a mild decrease in the flow of bile in all the dogs.

Four and 10 minims of the solution produced a marked decrease in urine and bile flow in all of the dogs.

11. Tainter, M. L.; Pedden, J. R., and James, M.: Comparative Action of Sympathicomimetic Compounds, J. Pharmacol. & Exper. Therap. **51**:371, 1934.

BASAL CELL CARCINOMA OF THE VULVA

REPORT OF FOUR CASES

JAMES M. WILSON, M.D.
DURHAM, N. C.

Considering all that has been written on the subject of carcinoma of the vulva, it is surprising to find that the basal cell type of tumor has received so little attention. This is particularly true when one considers its relatively benign nature in other parts of the body as compared with squamous carcinoma. That the tumor is uncommon is unquestioned; yet it occurs with sufficient frequency to warrant special consideration. The following study is based on the 4 cases reported here and on 23 additional cases collected from articles dealing with vulval carcinoma in general, found in the literature between 1916 and 1939. From this material an attempt is made to present data regarding the incidence, therapy and prognosis.

In order to clarify the term basal cell carcinoma the histopathologic picture must first be considered. Between the typical squamous carcinoma with its pearl-forming, large, clear cells and the classic basal cell tumor of Krompecher, there lies an intermediate group, referred to as "transitional cell" carcinoma, or *épithéliome intermédiaire*.[1] Within this group one sees variation all the way from one extreme to the other; it is the middle portion of the curve of expected biologic mutation of such a pleomorphic structure as the epidermis. For the sake of this discussion I have included the transitional cell carcinoma with the basal cell, largely because of the similar rarity of metastasis which it manifests; its greater radioresistance as compared with the typical basal cell tumor must be remembered, however. Not included in this discussion is the mixed basal and squamous cell carcinoma; because of its definite metastatic tendencies it must for practical purposes be considered a squamous cell carcinoma. It does occur on the vulva. Schreiner and Wehr[2] men-

From the Department of Obstetrics and Gynecology and the Department of Pathology, Duke Hospital.

1. Darier, J., and Ferrand, M.: Forme métatypique du cancer malpighien de la peau et des orifices muqueux, Ann. de dermat. et syph. **3**:385-406, 1922.

2. Schreiner, K., and Wehr, W. H.: Cancer of Vulva, with Report of One Hundred and Eighteen Cases, Surg., Gynec. & Obst. **58**:1021-1026 (June) 1934.

tioned 1 case, without details. Petit-Dutaillis [3] recorded 2, 1 of which was not followed; in the other the tumor recurred six months after a radical vulvectomy. It is, then, with this preliminary understanding that the following study is undertaken.

THE PRESENT STUDY

In 66,000 surgical specimens that have been examined in the department of pathology in the Duke hospital, carcinoma of the vulva has been diagnosed 32 times. Of the 32 tumors, 4 were of the basal cell type, an incidence of 12.5 per cent. The clinical data on cases 1 and 2 are available through the courtesy of the physicians who submitted the surgical material for study. Case 1 was subsequently observed here, when the patient was referred for roentgen therapy.

CASE 1.—Mrs. C. M., white, 58 years old, had passed the menopause nine years prior to examination. A small painless nodule had been present "at the edge of the vagina," in relation to the vulvovaginal gland, and had been slowly growing over a period of seventeen years. In the six months preceding operation it had rapidly increased in size, becoming ulcerated and painful. The condition of the inguinal nodes at that time is not known. Local excision with a wide margin was done. Seventeen months later she was referred to the Duke Hospital for treatment of a recurrence at the site of the original lesion. Over an area approximately 3 cm. in diameter she received 392 milligram hours of interstitial radium and 1,500 r of high voltage roentgen radiation over the perineum and the inguinal regions (formula: 170 kilovolts; 4 milliamperes; 40 cm.; filtration, 0.5 mm. each of copper and aluminum). She did not complete the course recommended. She was seen again nineteen months later, when no evidence of tumor could be demonstrated by physical examination, but four years after operation she is said to have died of local metastases to the bladder and rectum.

The surgical specimen (fig. 1 *A*) was an irregular mass of tissue measuring 8 by 6 by 6 cm. and covered on one surface by a 3 cm. fragment of skin. Centrally there was a firm white tumor mass measuring 4 by 4 by 5 cm. and surrounded by necrotic material containing small cysts.

Microscopic interpretation of the tumor was difficult. The large firm mass was obviously a fibroma. The necrotic cystic material appeared to be the vulvovaginal gland diffusely involved by an epithelial tumor, the larger "cysts" being dilated ducts lined with the neoplasm, some of them measuring as much as 0.5 cm. in diameter. In most of these the tumor seemed rather well circumscribed, but in many others it tended to invade the surrounding supporting stroma (fig. 1 *B*). In still other areas large and small masses of the carcinoma were seen apparently in no relation to any glandular structure, diffusely invading the surrounding tissue, even the superficial portion of the fibroma. Both types of growth showed more or less honeycombing, such as is seen in the cystic type of basal cell carcinoma. A small amount of brown pigment was scattered throughout, and in the superficial areas there was considerable evidence of acute and chronic inflammation.

3. Petit-Dutaillis, P.: Considérations sur le début, l'évolution et le traitement des épithéliomes primitifs de la vulve, d'après dix-sept cas observés et traités, Gynécologie **31**:65-81 (Feb.) 1932.

Histologically the tumor cells were rather closely packed, the outlines of the palely acidophilic cytoplasm being obscured. The nuclei were elongated and fairly dense and showed rather numerous mitoses. Nothing resembling pearl formation was noted. The tumor was classed as a transitional cell carcinoma of the basal cell type.

As to the origin of the tumor one can only guess. Certainly in some areas origin in the vulvovaginal gland was suggested, but its advanced state precluded

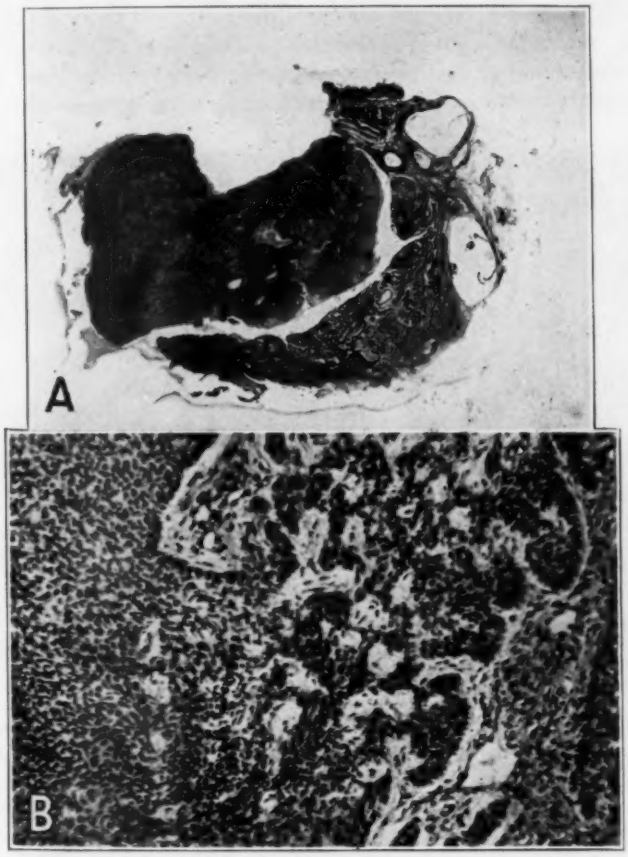


Fig. 1 (case 1).—*A*, lantern slide section, natural size, of the entire gross specimen. Note the edge of the skin (above); the fibroma (to the left), and the tumor of Bartholin's gland (to the right). Hematoxylin and eosin. *B*, invasion of the stroma where the large mass of cells breaks through the basement membrane of the gland. The growth is of the transitional cell type. Hematoxylin and eosin; × 127.

anything but speculation. Of particular interest, however, is the long-standing fibroma, a possible source of chronic irritation.

CASE 2.—Mrs. G. I., 47 years old, white, had in the past received intensive antisyphilitic therapy over a long period. A small growth had been present "in the vagina" for three years. This had been "sore" and had caused extreme nervousness, but only in the three months preceding operation had it begun to bleed and cause severe discomfort. Examination showed an indurated ulcer 3 cm. in diameter on the lower margin of the right labium majus. The right inguinal glands were tender but only slightly enlarged.

At the time of the biopsy extensive electrocauterization was done over the whole area, followed by (1) administration of 4,000 r in twenty-two days through a vaginal, an anterior and a posterior port (200 kilovolts; 20 milliamperes; filtration, 0.5 mm. of copper and 1 mm. of aluminum; 50 cm. distance) and (2) 2,000 r over the right inguinal region in twenty-eight days, the formula being the same

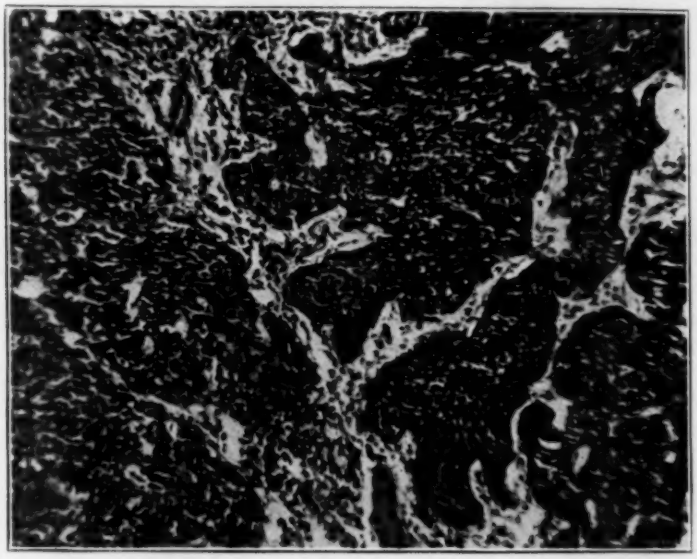


Fig. 2 (case 2).—Field showing a typical basal cell carcinoma. Hematoxylin and eosin; × 127.

except that a Thoraeus (copper, tin and aluminum) filter was substituted. However, there was early recurrence, and the patient died fifteen months after the first operation.

Histologically (fig. 2) the biopsy specimen showed ulceration of the epithelium with infiltration of the subcutis by masses of typical basal cells. The nuclei were oval, dark and sharply outlined and showed numerous mitoses. The depth of penetration into the deeper tissue could not be estimated.

CASE 3.—Mrs. E. R., 71 years old, white, had borne five children, all of whom were living. She had passed the menopause twenty-six years previously. A small itching pimple had been present on the anterior left labium majus for nine months, slowly increasing in size. It was slightly indurated, slightly elevated and grossly

ulcerated. The inguinal nodes were not enlarged. The diagnosis on biopsy was basal cell carcinoma, and a simple vulvectomy was done. Twenty-two months later the patient was in good health; there was no sign of local recurrence and no enlargement of the inguinal nodes.

On section the tumor was found to be superficial, measuring 2 cm. in diameter and from 1 to 3 mm. in thickness. Histologically (fig. 3) the cells were of the same type as those seen in case 1, even showing the same honeycombed arrangement. This growth, too, was designated as a transitional cell carcinoma of the basal cell type.

CASE 4.—Mrs. T. F., 59 years old, white, had borne six children, five of whom were living. She had passed the menopause nine years previously. She was first

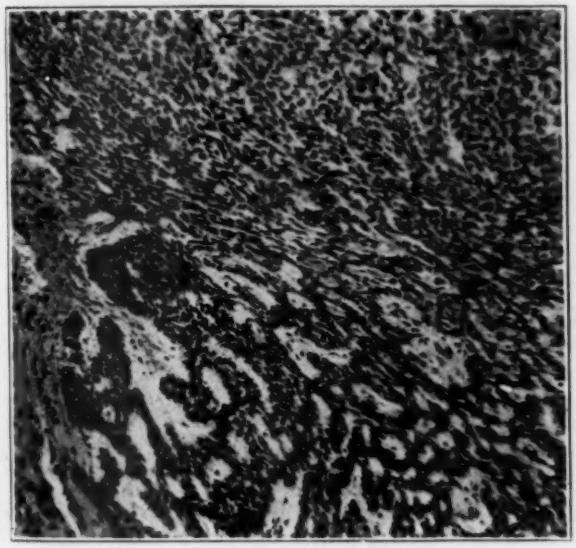


Fig. 3 (case 3).—Note the similarity of the cellular morphologic structure to that in figure 1 *B*. Hematoxylin and eosin; × 127.

seen in 1932, complaining of pruritus of one year's duration. A mild vaginal discharge was present. Biopsy of the cervix showed chronic cervicitis, which cleared up rapidly with simple douches. Six months later, because of persistence of the pruritus 160 milliampere minutes of roentgen therapy was given over the perineum. In 1935, because of continued discomfort, a partial vulvectomy was done, the left labium majus being removed. Eighteen months later she was found to have mild intertrigo in the left inguinal fold with continued pruritus in the left vulval region. From this area in 1939 a tiny superficial papillary nodule was removed under the impression that it was an epidermoid (sebaceous) cyst. Although it proved to be carcinoma, no further surgical or roentgen treatment was instituted, and there has been no recurrence in twenty months.

The gross surgical specimen measured but 2 mm. in its greatest diameter, and on serial section the tumor was thought to have been completely removed with

an adequate margin. Histologically (fig. 4) it presented a typical picture of cystic basal cell carcinoma, the nuclei being oval and dark and presenting numerous mitoses.

In only 17 of the 23 collected cases were sufficient clinical data for study recorded; these are listed in detail in table 1, together with the 4 cases reported here. One of the remaining 6 was mentioned by Temesváry [4] as being reported by Prytek; no reference was given. Thorough search of the literature has revealed no more than a mere mention of such a case in an article dealing solely with the histologic character of this

Fig. 4 (case 4).—Typical cystic basal cell carcinoma. Hematoxylin and eosin; × 127.

type of tumors [5]; no clinical details were given. Another case was mentioned by Mosto and Radice,[6] again with no clinical details. The remain-

4. Temesváry, N.: Ueber ein multiples Krompecher'sches Karzinom der Vulva, mit ausgedehenter Elephantiasis, Zentralbl. f. Gynäk. **50**:1575-1582 (June 12) 1926.

5. Prytek: Ueber die Plasmazellen bei Epitheliomen der Haut, Arch. f. Dermat. u. Syph. **120**:611-620, 1914.

6. Mosto, D., and Radice, J. C.: Tumores de vulva, benignos y malignos: Histopatología y consideraciones sobre 34 casos de tumores primitivos, Rev. med. y cien. afines **1**:33-51 (Nov. 30) 1939.

ing 4 were found among the 9 cases recorded by Göbel and Hamann;[7] no detailed information was given, and it is presumed that the patients died, whether or not of carcinomatosis is not known.

ANALYSIS AND COMMENT

Since each case or series of cases is lacking in certain details and since the total number is small, the following statistical studies are not entirely satisfactory. They are to be considered only as approximations, and in each analysis the possibility of misleading conclusions should be considered.

In an attempt to ascertain the incidence of the basal cell type of lesion the 5 cases of Prytek, Temesváry, Leigheb,[8] Claiborn and Holsinger[9] and Hinselmann[10] must be omitted; they are isolated, not being recorded in relation to a whole series. Table 2 shows the remaining cases, including those reported by Delporte and Cahen,[11] Eichenberg,[12] den Hoed[13] and Nuytten and Garraud.[14] It also includes by way of comparison the series of Schreiner and Wehr[2] and of Rentschler[15] and Tausch;[16] several other such series, which are not included, were found in the literature. The close approximation of the first 4 as compared with the others is startling, and, since it does not seem possible that the element of individual histologic interpretation could account for so wide a divergence, I am at a loss for a suitable explanation.

Regarding etiologic factors, I find that chronic irritation was known to have been present for a considerable time in 3 of my 4 cases; in none,

---

7. Göbel, A., and Hamann, A.: Zur Klinik und Therapie der Karzinome am äusseren Genitale, Zentralbl. f. Gynäk. **61**:1394-1419 (June 12) 1937.

8. Leigheb, V.: Epitelioma basocellulare superficiale della vulva dissimulato da fatti eczematoidi, Gior. ital. di dermat. e sif. **69**:1566-1572 (Dec.) 1928; cited by Claiborn and Holsinger.[9]

9. Claiborn, L. N., and Holsinger, H. B.: Basal Cell Carcinoma of Vulva, Surg., Gynec. & Obst. **54**:836-838 (May) 1932.

10. Hinselmann, H.: Ein sehr kleines Vulvakarzinom, Ztschr. f. Geburtsh. u. Gynäk. **103**:15-21, 1932.

11. Delporte, F., and Cahen, J.: Contribution à l'étude du traitement radio-chirurgical des épithéliomas de la vulve et de l'urètre, J. de chir. **41**:861-891 (June) 1933.

12. Eichenberg, H. E.: Beitrag zur Pathologie des Vulvakarzinoms, Ztschr. f. Geburtsh. u. Gynäk. **108**:276-302, 1934.

13. den Hoed, D.: Results Obtained in the Treatment of Malignant Tumors of the Vagina, Vulva and Urethra, Acta radiol. **17**:569-578, 1936.

14. Nuytten, J., and Garraud, R.: Valeur de la curiethérapie dans le traitement du cancer de la vulve, Gynéc. et obst. **36**:508 (Dec.) 1937.

15. Rentschler, C. B.: Primary Epithelioma of Vulva: Analysis of Seventy-One Cases, Ann. Surg. **89**:709-730 (May) 1929.

16. Tausch, M.: Beitrag zur Klinik und Statistic des Vulvakarzinoms, Monatschr. f. Geburtsh. u. Gynäk. **89**:402-419 (Dec.) 1931.

TABLE 1.—*Summary of Cases*

Date and Author	Author's Case No.	Patient's Age	Etiologic Factors	Location	Duration	Size	Inguinal Nodes	Therapy	Result	Life Span	Cause of Death	Autopsy	Type of Tumor
Wilson	1	58	Fibroma of labium for 17 years	In Bartholin's gland ?	6 mo.	8×6×6 cm.	?	Local excision; radium; high voltage irradiation	Died	4 yr.	Carcinoma	0	Transitional cell
Wilson	2	47	?	Right labium majus	3 yr.	3 cm.	Slightly enlarged bilaterally	Electrocautery; high voltage irradiation	Died	15 mo.	Carcinoma	0	Basal cell
Wilson	3	71	Obesity; intertrigo; no pruritus	Left labium majus	9 mo.	Diameter 2 cm.; thickness 3 mm.	Not enlarged	Simple vulvectomy	Living; no recurrence	22 mo.	.....	..	Transitional cell
Wilson	4	59	Pruritus for 7 years	Left labial region; labiectomy 4 years before	?	2 mm. diameter	Not enlarged	Local excision	Living; no recurrence	20 mo.	.....	..	Basal cell
1926 Temesváry	1	53	Recurrent erysipelas for 10 months	Multiple, on labia majora	? 10 mo.	Scattered nodules averaging 0.5 cm.	?	?	Died	3 mo.	Cardiac failure	0	Basal cell
1927 Leigheb [8]	1	68	Pruritus for 2 years; leukoplakia	?	? 1 yr.	?	Enlarged bilaterally, negative on pathologic examination	Radical vulvectomy	Died	7 days (postoperative)	Bronchopneumonia	..	Basal cell
1932 Claiborn and Holsinger [9]	1	69	Pruritus for 34 years	Left labium majus	? 6 yr.	3×2.5×0.6 cm.	Not enlarged	Local excision	Living; no recurrence	6 mo.	.....	..	Basal cell
1932 Hinselmann [10]	1	54	Pruritus for 7 years	Left labium majus	12 mo.	1.3×0.7×0.2 cm.	Not enlarged	Left labiectomy	?	?	.....	..	Photomicrographs suggest basal cell
1933 Delporte and Cahen [11]	10	40	?	On right from meatus to fourchet and into vagina	?	Very large; see "location"	Bilaterally enlarged; right positive on pathologic examination	Radium;* radical vulvectomy 14 mo. later	Died	17 mo.	Carcinoma	..	Basal cell
1933 Delporte and Cahen [11]	22	45	?	Periurethral extending into vagina 2 cm.	?	See "location"	Not enlarged	Radium, 8,125 mg. hours	Living; urinary incontinence	7 yr.	.....	..	Basal cell
1933 Delporte and Cahen [11]	24	80	?	Periurethral extending into vagina 5 cm.	?	See "location"	Not enlarged	Radium, 4,262 mg. hours	Died	8 mo.	Cardiorenal disease	0	Basal cell
1934 Eichenberg [12]	1	72	?	Right labium majus	1 yr.	"A small hand"	?	Radium, amount	Recurrence in	?	.....	..	Basal cell

1933 Delporte and Cahen [11]	22	45	?	Periurethral extending into vagina 2 cm.	?	See "location"	Not enlarged	Radium, 8,125 mg. hours	Living; urinary incontinence	7 yr.	.....	..	Basal cell
1933 Delporte and Cahen [11]	24	80	?	Periurethral extending into vagina 5 cm.	?	See "location"	Not enlarged	Radium, 4,262 mg. hours	Died	8 mo.	Cardiorenal disease	0	Basal cell
1934 Eichenberg [12]	1	72	?	Right labium majus	1 yr.	"A small hand"	?	Radium, amount unknown	Recurrence in 8 months	?	.....	..	Basal cell
1934 Eichenberg [12]	2	66	Pruritus for 10 years	Left labium minus	2 yr.	"A small hand," extended into vagina	Implied negative to pathologic examination at autopsy	"Excision"	Died	Death immediately postoperative	Pulmonary embolus	"No evidence of tumor"	Basal cell
1936 den Hoed [13]	1	?	?	?	?	?	?	?	Living; no recurrence	5 yr.	.....	..	Basal cell
1937 †Nuytten and Garraud [14]	5	66	Pruritus; duration ?	On left from clitoris to anus	4 mo.	See "location"	Bilaterally enlarged	Radium, amount unknown	Died	5 mo.	?	0	Basal cell
1937 †Nuytten and Garraud [14]	16	40	?	Left labium and cervix	?	?	Slightly enlarged on left	Radium and high voltage irradiation; amount not clear	Vulval recurrence 8 months; extension of cervical lesion	?	.....	..	"Malpighian epithelioma with tendency to basal cell type"
1937 Göbel and Hamann	12 (table 5)	77	?	Right labium minus	?	?	Not enlarged	Operation; radium, amount unknown	Died	14 mo.	Bronchopneumonia	No evidence of carcinoma	Basal cell
1937 Göbel and Hamann	3 (table 6)	62	?	Meatus	2 yr.	?	Not enlarged	Electrocoagulation	Recurrence in 13 mo.; therapy repeated; living	14 yr.	.....	..	Basal cell
1937 Göbel and Hamann	5 (table 6)	70	?	Left labium majus	2 mo.	?	Enlarged on left	Electrocoagulation	Living; no recurrence	13 yr.	.....	..	Basal cell
1937 Göbel and Hamann	6 (table 6)	73	?	Clitoris	? 120 mo.	?	Enlarged bilaterally	Electrocoagulation	Living; no recurrence	10 yr.	.....	..	Basal cell
1937 Göbel and Hamann	9 (table 6)	51	?	Clitoris	3 mo.	?	Enlarged on left	Tumor with radium needles, nodes with roentgen therapy; amounts not stated	Living; no recurrence	5 yr.	.....	..	Basal cell

* See original publication.

† Three other cases of "épitheliome malpighien du type intermédiaire" are listed (cases 4, 6 and 11); as it is not clear what this term means, they are not included in table 1. All 3 patientts were treated with radium. In cases 4 and 11, in which the tumors occurred on the labia, the patients died the second day after needling. In the third (case 6), a case of tumor of the urethral meatus, the patient was living five years after treatment (10.08 millicuries destroyed) without recurrence.

however, was there leukoplakia. Of the 17 collected cases, in only 6 were etiologic factors suggested and in only 1 was leukoplakia mentioned. This is especially interesting when one considers that basal cell tumors almost never arise from leukoplakia of mucous membranes (e. g., those of the mouth), their most common origin being from the waxy hyperkeratoses of the face.

Table 3, which shows the site of origin, is self explanatory.

TABLE 2.—*Incidence*

Series	Total Number of Vulval Carcinomas	Number of Basal Cell Carcinomas	Percentage of Basal Cell Carcinomas	Number of Mixed Basal and Squamous Cell Carcinomas	Percentage of Mixed Basal and Squamous Cell Carcinomas
Duke Hospital	32	4	12.5	0	0
Delporte and Cahen	25	3	12.0	0	0
Nuytten and Garraud	17	2	11.8	0	0
Göbel and Hamann	61	9	14.7	0	0
Eichenberg	114	2	1.7	0	0
den Hoed	41	1	2.4	0	0
Mosto and Radice	21	1	4.7	0	0
Schreiner and Wehr	118	0	0	1	0.8
Rentschler	71	0	0	0	0
Tausch	54	0	0	0	0

TABLE 3.—*Site of Predilection*

Labia Majora	Labia Minora	Meatus	Clitoris	Bartholin's Gland
11	2	3	2	1 (?)

TABLE 4.—*Condition of Inguinal Nodes*

		Enlarged			
Not Enlarged	Status Unknown	Unilateral	Bilateral	Proved Positive	Proved Negative
8	4	3	3	1	2

There is no essential difference in this respect from squamous carcinoma. I may note here that both the tumors arising on the clitoris and 2 of the 3 which took origin at the meatus showed no recurrence in periods ranging from five to fourteen years.

The status of the inguinal nodes is shown in table 4.

In only 3 of 9 cases in which enlargement was present was histologic examination done. In the single case in which the inguinal nodes were involved the original lesion was very large, and the possibility of direct extension rather than lymphatic metastasis must be considered. It should be noted also that 3 patients with enlarged nodes lived beyond the five year limit, only 1 of whom received irradiation over the nodes.

Table 5, showing the mortality rate, is the most important and least satisfactory of all. For the sake of accuracy I must include the 4 cases of Göbel and Hamann not shown in table 1, making a total of 25; these authors listed in detail only their autopsies and five year cures, so that the remainder of the patients must be presumed to be dead.

The statistical picture is not bright, the five year salvage being only 24 per cent. Although 20 per cent of the patients died of causes other than carcinoma, 2 of the 5 deaths were postoperative and are therefore useless as follow-ups. And, while only 12 per cent of the patients are known to have died of carcinoma, 2 of the 3 listed under "status questionable" showed recurrence when last seen. To these must be added the 4 patients of Göbel and Hamann, making a total of at least 9, or 36 per cent, to be considered as having died of cancer.

The foregoing figures, however, must be interpreted in the light of certain other facts. Owing to the advanced age of most of the patients (average 60 years), the expected death rate from other causes will cut

TABLE 5.—*Mortality Statistics*

	Status Questionable	Died of Carcinoma	Presumed Dead *	Died of Other Causes	Died; Cause Unknown	Living Less than Five Years	Living More than Five Years
Number.....	3	3	4	5	1	3	6
Per cent.....	12	12	16	20	4	12	24

* The 4 patients of Göbel and Hamann, previously mentioned.

down the possible five year salvage. In addition, the two factors of duration and size of the tumor have a definite bearing on the outlook. The known biologic characteristics of slow growth and infrequency of metastasis constitute an incontrovertible fundament for a fair prognosis. This is borne out by the series of Göbel and Hamann, which contains the largest number of basal cell tumors; analysis of their figures shows a five year salvage of 44 per cent, obtained, as Taussig [17] has shown, with what would constitute woefully inadequate therapy in the case of squamous carcinoma.

Regarding the type of treatment indicated, only generalization can be made. I do not feel that the radical Basset type of operation advocated by Taussig is indicated in cases of basal cell carcinoma. On the other hand, the figures just cited should give the surgeon a healthy respect for the tumor and prevent his judgment from being lulled into a false sense of security by the biopsy report of a basal cell lesion; vulval carcinoma is notoriously treacherous. Surgical intervention, irradiation and electrocautery have all given good results, the last

17. Taussig, F. J., in Pack, G. T., and Livingston, E. M.: Treatment of Carcinoma and Allied Diseases, New York, Paul B. Hoeber, Inc., 1940, vol. 2, p. 1789.

especially in the hands of the German school. Common sense requires that in each case one take into consideration the size, duration and accessibility of the lesion; the operative risk, and the skill of the surgeon. With the possibility of good plastic repair, I personally advocate wide excision by the scalpel. When the meatus is involved or when the growth has extended to any degree into the vagina, radium or roentgen therapy seems logical. Each case must be individualized.

SUMMARY

Four cases of primary basal cell carcinoma of the vulva are reported, together with 23 cases collected from the literature.

The general incidence varies considerably, being 12 per cent of 32 primary vulval carcinomas at the Duke Hospital.

The death rate from the tumor itself is estimated to be at least 36 per cent in the entire series.

It is felt that, while the condition is serious, it carries a better prognostic import than does the squamous cell lesion.

I do not believe that the radical Basset operation is indicated. It is my opinion that when possible wide local excision should be done.

Attention is called to the transitional cell type of carcinoma, which, like the basal cell carcinoma, metastasizes infrequently.

SPINOTHALAMIC TRACTOTOMY IN THE MEDULLA OBLONGATA

AN OPERATION FOR THE RELIEF OF INTRACTABLE NEURALGIAS OF THE OCCIPUT, NECK AND SHOULDER

JAMES C. WHITE, M.D.

BOSTON

Not infrequently the neurosurgeon is confronted by a case of intractable pain distributed so high over the shoulder and neck that it cannot be interrupted by cordotomy, no matter how high the spinothalamic tract is sectioned in the cervical portion of the spine. Pain of this type is most often due to neuralgia arising in an amputation stump of the upper part of the arm or shoulder or caused by avulsion or carcinomatous infiltration of the brachial plexus or to one of the rare unexplained neuralgias which may follow an operative incision or a penetrating wound of the neck or upper part of the back. As is well known, such conditions have been most difficult to relieve, even with extensive resection of the posterior cervical sensory roots and the consequent sacrifice of a useful arm.

It has been observed clinically in patients with thrombosis of the posterior inferior cerebellar artery (fig. 1) that loss of pain and temperature sensation usually involves the entire opposite side of the body, as well as the ipsilateral side of the face (Wechsler[1]). The reason for this is that the descending trigeminal root (uncrossed) and the spinothalamic tract (crossed) lie side by side in the lateral part of the medulla, between the inferior cerebellar peduncle (restiform body) and the inferior olive. Both are included in the area of thrombosis. The descending trigeminal tract lies just dorsal to the vagal rootlets which emerge at this point, whereas the spinothalamic tract lies just ventral to and between the emerging vagal rootlets and the olive (figs. 2 and 3). These figures also show that the tract is relatively accessible to surgical division at this level. As in the spinal cord, only a thin layer of fibers of Gowers' indirect spinocerebellar tract lies peripheral to it. The rubrospinal tract and the descending root of the fifth cranial nerve are situated dorsally and the inferior olivary nucleus ventrally. Medially

From the Neurosurgical Service of the Massachusetts General Hospital.

1. Wechsler, I. S.: A Text-Book of Clinical Neurology, ed. 2, Philadelphia, W. B. Saunders Company, 1933, p. 368.

in the reticular substance lie the nucleus ambiguus (voluntary motor nucleus of the vagus), the dorsal accessory olivary nucleus and the descending sympathetic axons. The olivocerebellar fibers traverse this area. From all that is known, no appreciable disability should be produced if some of these fibers or even some of the substance of the dorsal, or inferior, olive should be cut. This is likewise true of injury to Gowers' tract, which is severed at every spinal section of the spinothalamic tract, and also of injury to the rubrospinal tract. The important pyramidal tract lies ventral to the inferior olive, where it is well protected from injury considering its vulnerable position in the spinal cord.

Fig. 1.—Infarction of medulla after thrombosis of the posterior inferior cerebellar artery on the right side. (From Wechsler's "Text-Book of Clinical Neurology," [1] by permission of W. B. Saunders Company.)

The anatomic position of the spinothalamic tract at different levels is best illustrated in Walker's [2] study of its degenerated axons (fig. 4). Above the restiform body (fig. 4 *B*) the tract occupies a much deeper position beneath the cerebellar peduncles, but it again comes close to the surface of the brain stem in the mesencephalon, at the point where the trochlear nerve roots are given off (fig. 4 *A*). This is at the level

2. Walker, A. E.: The Spinothalamic Tract in Man, Arch. Neurol. & Psychiat. **43**:284-298 (Feb.) 1940.

of the tentorium, and the tract has been interrupted here by Dogliotti.[3] Exposure of the brain stem at the incisura of the tentorium is deep. Dogliotti's 3 surviving patients were freed of pain but complained of "unpleasant and undetermined feelings (paresthesias) diffused to the half of the body opposite to the side operated on." To the surgeon with experience in operations in the posterior fossa and especially in the

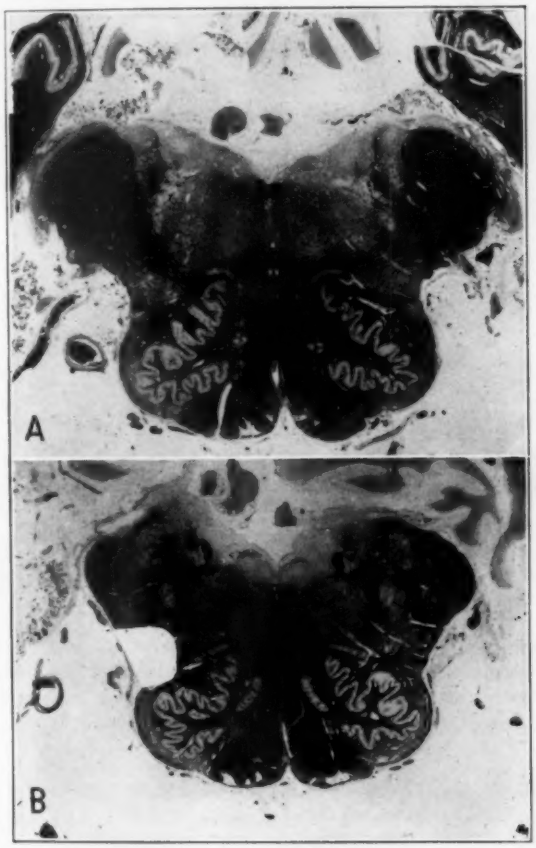


Fig. 2.—*A*, cross section of the medulla oblongata at the point of emergence of the ninth and tenth cranial roots. On the left side the posterior inferior cerebellar and vertebral arteries are shown close to the side of the medulla, as was the situation in the case described here. *B*, the medulla just below the last vagal rootlet, the level at which the spinothalamic tract was sectioned. The area cut across is illustrated in white. In this section the vertebral artery is situated more laterally, rather than pressed against the side of the inferior olive, as is usually the case.

3. Dogliotti, M.: First Surgical Sections, in Man, of the Lemniscus Lateralis (Pain-Temperature Path) at the Brain Stem, for the Treatment of Diffused Rebellious Pain, Anesth. & Analg. **17**:143-145, 1938.

trigeminal tractotomy devised by Sjöqvist,[4] a medullary section of the spinothalamic tract between the levels illustrated in figures 4 *C* and 4 *D* would seem to be a more practical procedure.

This operation was first performed by Schwartz, of St. Louis, and the case was reported by Schwartz and O'Leary [5] at the meeting of the Society of Neurological Surgeons in April 1940. Unfortunately, their patient, who suffered from advanced malignant disease, failed to survive the operation for more than a few days, but it was possible to make a fairly satisfactory postoperative neurologic examination. This showed the expected high level of analgesia and thermoanesthesia, with no visible impairment of other important tracts. In this article there is a brief added note about a second patient in whom Dr. Schwartz cut the left spinothalamic tract at the level of the inferior olive. This fully

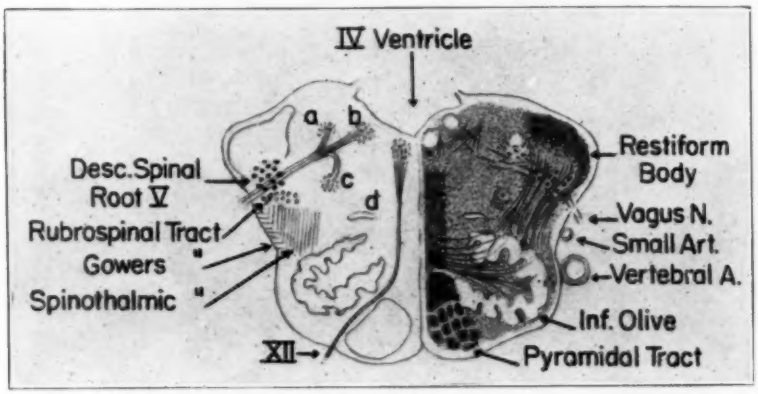


Fig. 3.—Drawing to illustrate the position of the more important nuclei and fiber tracts in the medulla. Note (*a*) the tractus solitarius; (*b*) the dorsal motor nucleus of the vagus nerve (autonomic); (*c*) the nucleus ambiguus (voluntary motor nucleus), and (*d*) the dorsal accessory olivary nucleus.

eliminated pain in the chest, shoulder and axilla caused by metastases from carcinoma of the breast. No complications from injury to neighboring structures were observed.

The case to be reported corroborates the observations of Schwartz and O'Leary, except that an otherwise perfect result was complicated by cerebellar ataxia. This complication, as will be pointed out later,

4. Sjöqvist, O.: Studies on Pain Conduction in the Trigeminal Nerve: A Contribution to the Surgical Treatment of Facial Pain, Acta psychiat. et neurol., 1938, supp. 17, pp. 1-139.

5. Schwartz, H. G., and O'Leary, J. L.: Section of the Spinothalamic Tract in the Medulla with Observations on the Pathway for Pain, Surgery **9**:183-193, 1941.

can probably be avoided, and the operation then will constitute a brilliant application of knowledge gained from neuroanatomic investigation to the neurosurgical treatment of pain. The opportunities for relieving a number of hitherto intractable painful syndromes opened up by a practical method of sectioning the spinothalamic tract in the brain stem are so far reaching that further experience with this method is of con-

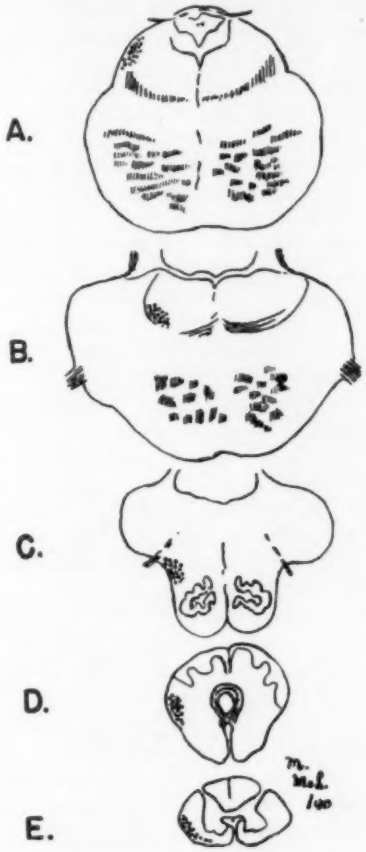


Fig. 4.—The position of the spinothalamic tract at various levels of the brain stem and spinal cord, according to Walker.[2] *A*, upper part of pons; *B*, lower part of pons; *C*, medulla oblongata at the level of the olive; *D*, lower part of the medulla; *E*, second cervical segment of the spinal cord.

siderable importance. This is the reason for the following detailed account of a young woman in good general condition who has recovered from the operation and has been freed of intractable neuralgia of the neck, shoulder, arm and upper part of the chest of three years' duration. It is unnecessary to give a separate description of the operative technic; it will be presented as it was carried out in this patient.

REPORT OF A CASE

J. S., an otherwise healthy woman of 29, had been admitted to the peripheral circulatory disease clinic of the Massachusetts General Hospital for Raynaud's disease in 1935 and was the first patient to be subjected to a preganglionic sympathectomy of the upper extremities. This operation, which has been developed by Smithwick,[6] was performed in two stages through posterior paramedian incisions, with removal of short lengths of the central ends of the third ribs and transverse processes. The sympathetic trunk was cut across on each side beneath the third thoracic ganglion, and its cephalic end was drawn up and buried in the second intercostal muscle. In order to interrupt additional vasoconstrictor fibers which emerge in the second and third intercostal nerves, Dr. Smithwick at first resected short segments of these two nerves at their point of exit from the intervertebral foramens, the portion which gives off the sympathetic rami communicantes. Experience with this method soon taught that regeneration of the vasoconstrictor fibers would take place unless the intercostal nerves were freed centrally far enough to permit resection of a portion of their anterior roots. Regeneration of vasoconstrictor activity with recurrent manifestations of Raynaud's disease took place in this woman within six months, and the symptoms were so severe that she demanded further operation. In an attempt to secure permanent interruption of the vasoconstrictor fibers, Dr. Smithwick reoperated on several occasions and attempted to resect the cicatricial tissue and sympathetic fibers regenerating from the intervertebral foramens.[7]

In September 1937, after these operations, the patient began to complain of neuralgic pain down the inner side of the upper part of the right arm and in the right axilla.[8] In its early stages the pain was confined to the territory of the divided nerve trunks, but by the autumn of 1938 it was beginning to involve more of the right arm and breast and was becoming increasingly severe. It was observed that on the painful side the patient had a warm, dry hand, whereas the left hand was frequently cold, moist and cyanotic. After consultation (requested by Dr. Smithwick) she was admitted to the neurosurgical service for spinal root section.

On Oct. 4, 1938, laminectomy was performed, with section of the posterior sensory roots of the second and third intercostal nerves on the right (neuralgic) side and of the corresponding anterior motor roots on the left, in the hope of securing permanent interruption of the vasoconstrictor fibers. As the second and third intercostal nerves were the only ones which could have been exposed to trauma at Dr. Smithwick's previous operations, we had anticipated that division of their sensory roots would bring relief from the neuralgic pain. In this we were completely mistaken, and her pain was in no way alleviated, although circulation in the hand has continued at a maximum on the side where the anterior roots with their vasoconstrictor fibers were cut. The neuralgia not only persisted but increased in severity and spread to involve the entire arm, upper part of the chest, neck and occiput on the right side. This area became hyperesthetic and so painful on touch or movement that the patient was no longer able to use the arm and had to hold it constantly in a guarded position. During the past summer she

6. Smithwick, R. H.: Surgical Intervention on the Sympathetic Nervous System for Peripheral Vascular Disease, Arch. Surg. **40**:286-306 (Feb.) 1940.

7. The circulatory aspects of the case of J. S. have been summarized by Smithwick.[6]

8. Neuralgia following this operation has never been observed in any other patient.

required increasing doses of codeine sulfate and phenobarbital and stated on numerous occasions that self destruction would be preferable to her neuralgic pain.

In this highly neurotic condition she was seen in consultation by Dr. Stanley Cobb, chief of the psychiatric service, who stated that in his opinion her pain was an organic neuralgia and not of functional origin. The possibility of relieving this high cervical and brachial neuralgia by cutting the spinothalamic tract in the medulla was then discussed with the patient, with an explanation of the risks of injury to contiguous structures. She accepted this without hesitation and furthermore agreed that she would do everything in her power to go through the operation under local anesthesia, in order to make certain that the section should be carried to a sufficient depth to insure analgesia to the first cervical segment.

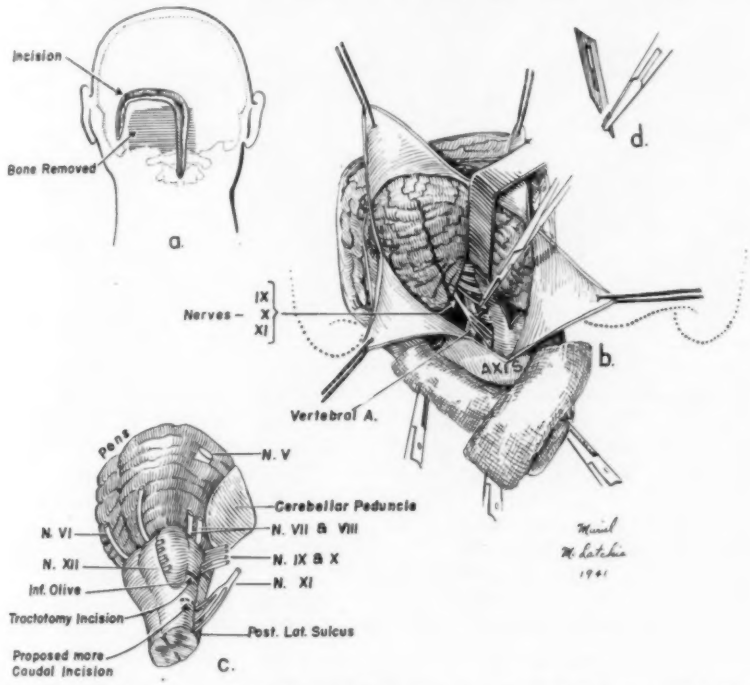


Fig. 5.—Technic of spinothalamic tractotomy in the medulla. *a*, scalp incision and extent of occipital bone to be removed. *b*, exposure of the structures at the side of the medulla and insertion of the knife in the posterior lateral sulcus. *c*, medulla and pons viewed from below and from the side to show the relation of the tractotomy incision to the vagal rootlets and the inferior olive. In future cases it is planned to divide the tract at a more caudal level, indicated by the broken line. *d*, adaptation of the pointed Bard-Parker blade into a chordotomy knife. The large central portion of the blade is broken off, leaving only 4 mm. of tip protruding from the hemostat.

This operation was performed on Oct. 9, 1940, with the patient in the prone cerebellar position. After preliminary infiltration of procaine hydrochloride solution (1 per cent, with epinephrine hydrochloride) into the occipital region and along the posterior borders of both sternocleidomastoid muscles, a cerebellar

incision was made in the scalp on the left side and the occipital bone rongeured away from 2 cm. to the right of the midline to a point just medial to the mastoid air cells on the left side and from the insertion of the occipital muscles above down into the foramen magnum below (fig. 5 *A*). The dura over this area was opened widely and the cisterna magna drained. On elevating the cerebellar tonsil it was then possible to obtain a clear view of the side of the medulla and the roots of the spinal accessory, vagus and glossopharyngeal nerves at their points of exit from the upper cervical portion of the cord and the posterior lateral sulcus of the medulla (fig. 5 *B*). The point selected for making the section lay just below (caudal) and ventral to the last vagal rootlet (fig. 4 *C*). My purpose had been to incise to a depth of 4 mm. straight inward from this point and anteriorly to the inferior olive, but the large trunk of the vertebral artery obscured the lateral bulge of the olive. In addition, another good-sized arterial trunk lay just below the emerging vagal rootlets and adhered to the surface of the medulla (figs. 2 *A* and 3). This must have been a large branch of the posterior inferior cerebellar artery. At first it looked as though it would be impossible to dislodge it and make the cut at the necessary point, but by gentle wiping with a wisp of cotton held in a thin-bladed forceps it was finally possible to displace it forward. It was then a relatively simple matter to make the incision in the posterior lateral sulcus (fig. 5 *C*). The vagal rootlets mark this point and are just as satisfactory a marker as the dentate ligament in the cord, except that they can be neither grasped nor stretched with impunity. A good instrument for making this incision is a pointed Bard-Parker knife blade held at right angles in a small hemostat and broken off so that the point protrudes exactly 4 mm. (fig. 5 *D*). Using this instrument, I thrust the point directly inward just short of its measured depth and cut ventrally down to the vertebral artery, which obscured the lateral edge of the inferior olive. By angulating the point still farther inward and ventrally I felt that I was able to carry the cut well down to the level of the olivary nucleus (figs. 2 *B* and 5 *C*). The patient, who remained fully conscious, was then tested, and a sensory level was established at the shoulder girdle. The knife blade was then reinserted to its full depth. After this it was found that pricking with a needle was no longer painful in the shoulder and neck. During the first cut she had made no mention of any painful sensation, but the second time the knife entered at the posterior lateral sulcus she complained momentarily of a sharp sensation in the ipsilateral side of her face—presumably from touching the ventral fibers of the descending trigeminal tract. This and some twinges of pain referred to her ear as the vagal rootlets were put on a stretch were the only sensations which she mentioned. As soon as the spinothalamic tract on her left side had been cut she could tell that the pain in her right arm had vanished. The cut caused almost no bleeding, and by additional good fortune it had been possible to keep the field dry throughout this critical part of the operation. The patient's pulse and blood pressure had remained steady throughout the procedure. A routine closure of the muscles, fascia and skin was carried out with multiple layers of interrupted silk sutures, and the patient was returned to her bed in excellent condition.

Recovery from operation was uneventful except for headache lasting five days and a mild depressive psychosis. It was difficult to persuade her to take adequate amounts of liquids and solids or to resume normal physical activity, but this abnormal behavior was less exaggerated than after previous operations. She urinated spontaneously on the evening of the day of operation and noted no difficulty in swallowing and no change in the quality of her voice. During her early convalescence it was impossible to detect any evidence of injury to the cranial nerves or to the spinal pathways other than the spinothalamic tract. In view of

the fact that during the tractotomy she had complained of pain in the left side of her face (indicative of trauma to the descending trigeminal tract), it is surprising that no change in pain or thermal sensation could be discovered in this area afterward. She was discharged from the hospital relieved of her old complaints on the twenty-fourth day after operation.

As long as the patient remained in bed no signs of injury to cerebellar function were observed except for very slight past pointing to the left (the side on which the brain stem was incised). After she became ambulatory, however, she complained of a sense of forced swaying to the left, so that in walking she had to prevent herself from falling by touching a wall or holding another person's arm. When she returned to the hospital for reexamination, three months later, her gait was still too unsteady to permit her to walk across a room without support. There was also a tendency to past point about 1 inch (2.5 cm.) to the left in lowering her arm from a vertical to a horizontal position with her eyes closed. When she was "off her feet" all sensation of unsteadiness disappeared and she was able to carry on complicated synergic movements, such as typing, with her former facility.

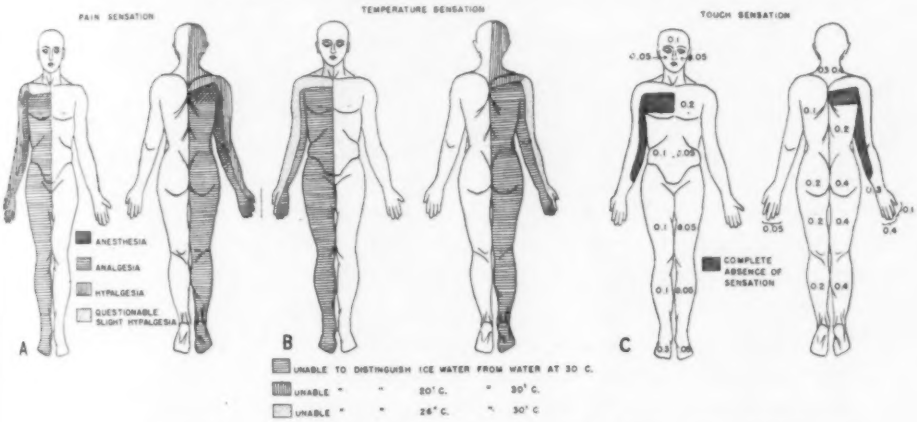


Fig. 6.—Results of tests for pain, temperature and touch. The figures are recorded in grams and represent the minimal pressure of Frey's hairs which could be felt. *A* and *B*, tests made on Oct. 23, 1940. *C*, test made on October 24. See text for fuller explanation.

(This difficulty in gait, even if it lasts, should not interfere with any occupation at which the patient can remain seated. It is probable that it will disappear in time, as is usually the case after such severe disturbances following injury to the lateral cerebellar structures by abscess of the brain or trauma, but it must be admitted that the improvement to date has been slight.)

From the moment the spinothalamic tract was cut the long-standing neuralgia disappeared. At the time of writing, analgesia and thermoanesthesia have remained complete below the sixth cervical segment, and there has been a definite reduction in these modalities of sensation as high as the first cervical segment. The patient is convinced that she remains fully relieved and fails to detect any disagreeable sensation on using her arm or on strenuous massage of the hitherto hypersensitive area in the upper part of her chest, her arm and her neck.

Before her discharge from the hospital, careful neurologic tests were performed to determine changes in the various forms of sensation over her entire

body. Tests for discrimination of pain, temperature and touch were carried out in a rough quantitative manner, and the results are shown in figure 6. These show complete anesthesia over the second and third thoracic spinal nerves on the right side, corresponding with the previous posterior rhizotomy. As a result of section of the spinothalamic tract, pain and temperature sensation have been completely interrupted below the sixth cervical segment and impaired over the posterior part of the scalp and the neck, but only to a minor degree over the front of the neck, shoulder and outer arm (fig. 6*A* and *B*). Figure 6*C* shows only a minimal reduction in tactile acuity (measured by the Frey hairs) on the side deprived of its spinothalamic innervation. This difference was too slight for the patient to notice subjectively. No change in deep pressure, vibration or position sense could be made out. These tests were repeated at her subsequent admission (three months after operation) and showed no recovery of sensation. The changes are consistent with the well known effects of cutting the pain and temperature pathway in the spinal cord.

COMMENT

The operation described was the first recorded successful spinothalamic tractotomy carried out in the medulla oblongata. Credit for suggesting this procedure belongs to Drs. Schwartz and O'Leary,[5] of St. Louis. Although the first patient operated on by Dr. Schwartz failed to recover, the period of survival was long enough to demonstrate a satisfactory high loss of pain and temperature sensation without any serious injury to neighboring tracts and nuclei. It is of particular interest to know that this patient left her bed unassisted a few hours after operation without any disturbance in gait being recorded. In Sjöqvist's trigeminal tractotomy there is a definite risk of producing cerebellar disturbances due to the propinquity of the descending trigeminal tract to the inferior cerebellar peduncle (Rowbotham[9]). Involvement of this sort after the more ventral incision of the brain stem which was used to divide the spinothalamic tract was not anticipated. Whether it was due to injury of the restiform body, to the olivocerebellar fibers or to their blood supply is not certain. As Grant and Weinberger[10] have found that disturbances of this sort after section of the descending spinal trigeminal root can be reduced by making a more caudal incision, it will be advisable to try this modification in the future. The incision, instead of being made ventral to the posterior lateral sulcus just caudal to the last emerging vagal rootlet, should be placed 5 to 8 mm. caudal to this point, i. e., just below instead of just above the tip of the fourth ventricle (obex). Although it is probable

9. Rowbotham, G. F.: Treatment of Pain in the Face by Intramedullary Tractotomy, Brit. M. J. **2**:1073-1076, 1938.

10. Grant, F. C., and Weinberger, L. M.: Experiences with Intramedullary Tractotomy: I. Relief of Facial Pain and Summary of Operative Results, Arch. Surg. **42**:681-692 (April) 1941.

that postoperative cerebellar disturbances will disappear spontaneously in time, they are a serious defect in a person who is able to lead an active life.

I have compared notes about the operation with Dr. Schwartz, and both of us have reached the conclusion that the landmarks for cutting the tract are just as well defined in the medulla as in the spinal cord. The pyramidal tract is protected by the interposed mass of the inferior olive. In medullary tractotomy care must be taken not to traumatize the vagal rootlets, which has resulted in temporary inferior laryngeal paralysis in some cases of descending spinal trigeminal root section reported by Sjöqvist.[4] As far as is known, injury to the neighboring rubrospinal tract or to either the main inferior olivary nucleus or the dorsal accessory olive will not cause any serious disturbance. Whether injury to the nucleus ambiguus from too deep a section would result in difficulties in swallowing is not certain, but, since this nucleus is a relatively long structure, injury to a small group of its motor neuron cells should not result in any lasting disability. Other uncertain points are the exact position of the motor fibers to the bladder and the risk of injuring them. In this case the patient voided spontaneously within a few hours of the operation. The fact that the patient did not have Horner's syndrome or any alteration in sudomotor or vasomotor activity shows that the incision did not penetrate the reticular substance to a sufficient depth to injure the descending sympathetic fibers which are supposed to lie in this area (List and Peet,[11] Foerster,[12] Magoun [13]). Judging from this single experience, it would not seem that spinothalamic tractotomy in the medulla offers any great difficulty or danger, and it is quite possible that it may prove to be as simple a procedure as section of the tract in the spinal cord.

The one major difficulty encountered by both Dr. Schwartz and myself lay in dealing with the vessels that lie alongside this region of the medulla. In this patient a large vertebral artery obscured the bulge in the medulla that marks the inferior olive and so filled the space between the medulla and the bony wall of the foramen magnum that it could not be dislodged (fig. 3). There was another awkward arterial trunk of considerable size which ran just ventral to the glossopharyngeal and vagal rootlets and was adherent to the side of the medulla at the

---

11. List, C. G., and Peet, M. M.: Sweat Secretion in Man: V. Disturbances of Sweat Secretion with Lesions of the Pons, Medulla and Cervical Portion of Cord, Arch. Neurol. & Psychiat. **42**:1098-1127 (Dec.) 1939.

12. Foerster, O.: Die vegetativen supranuclearen Bahnen und die Reflexe der vegetativen Sphäre, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 5, p. 213.

13. Magoun, H. W.: Descending Connections from the Hypothalamus, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:270-285, 1940.

point where the section had to be made. This appeared to be a large branch of the posterior inferior cerebellar artery. In addition to this there were a number of smaller vessels, one of which was clipped and cut. It was finally possible to wipe the larger artery out of the way. Had this not been the case or had it been injured and bled, I believe that it could have been clipped without causing widespread ischemia of the medulla, because the point for introduction of the cordotomy knife lay below (caudal to) its important tributary branches to the inferior cerebellar peduncle (restiform body) and the vestibular nuclei. The importance of handling these vessels skilfully to insure complete hemostasis and to avoid profuse bleeding, which might involve serious trauma to the medulla and its cranial nerve roots, cannot be overemphasized. Routine inspection of this region in all the operations on the posterior fossa performed during the past five months has convinced me that the lateral surface of the medulla down to the bulge of the olive can be safely exposed in the average patient but that in an exceptional case in which the blood vessels are unusually large this step may be extremely difficult.

One further point deserving consideration is the reason for the incomplete loss of pain and temperature sensation above the seventh cervical segment. This fortunately turned out to be for the best, as the patient retained these forms of sensation in the outer part of the arm, the neck and the scalp to a large degree, but with loss of her former hyperesthesia in these areas. The explanation for this incomplete loss must depend on the anatomic arrangement of the pain fibers in the spinothalamic tract. According to Foerster,[14] the fibers are arranged in a laminated fashion, those from the lowermost segments of the body occupying a place at the periphery of the tract and those of the higher segments remaining closer to the central gray matter (fig. 7 *A*). If this theory is correct, one must conclude that cutting to a depth of 4 mm. was not deep enough to secure complete interruption of the central portion of the tract. On the other hand, Hyndman and Van Epps[15] and also Walker[2] have presented evidence in favor of a different composition of the tract. According to them, the fibers from the lowest body segments lie in the more dorsal portion of the tract, whereas those from higher segments are more ventrally placed (figs. 7 *B* and *C*). In describing the spinothalamic tract in the bulb Walker stated that "there is both anatomical and clinical evidence for suggesting a topical arrangement within the tract at this level. The fibers which carry sensory

14. Foerster, O.: Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände, Berlin, Urban & Schwarzenberg, 1927.

15. Hyndman, O. R., and Van Epps, C.: Possibility of Differential Section of the Spinothalamic Tract, Arch. Surg. **38**:1036-1053 (June) 1939.

impulses from the caudal parts of the body lie laterally (peripherally) and dorsally; those from the head are more medially and inferiorly situated." As the exact level of the olive, which marks the ventral limits of the tract, was obscured by the vertebral artery, it is quite possible that these most ventrally situated fibers were not completely divided. Until this problem is settled it will be essential to perform this operation under local anesthesia and to make progressively deeper and more ventral sections into the medulla until the desired sensory level is obtained.

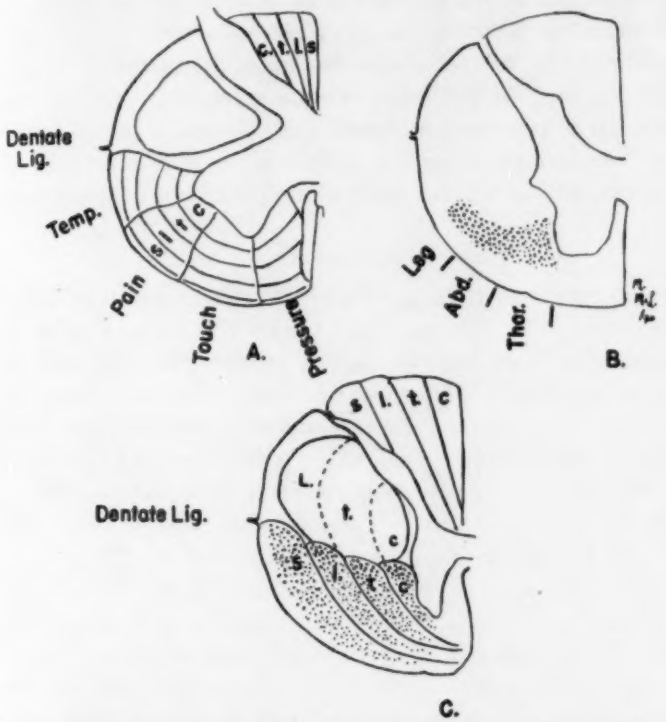


Fig. 7.—Anatomic composition of the spinothalamic tract according to: (*A*) Foerster; (*B*) Hyndman and Van Epps and (*C*) Walker. Abbreviations used in representing the segmental fibers: *c*, cervical; *t*, thoracic; *l*, lumbar; *s*, sacral. In Walker's diagram the heavy stippling in the most dorsal portion of the spinothalamic tract represents the hypothetic position of the temperature fibers. The most medial and ventral fibers are supposed to carry touch and pressure impulses.

Intramedullary section of the spinothalamic tract should make it possible to relieve a number of hitherto intractable painful syndromes of the shoulder, neck and occiput. These include the neuralgias which may follow amputation of the upper extremity and avulsion of the brachial plexus, and certain obscure painful states which occasionally develop after penetrating injuries and operations in this area. Even

the most extensive resection of posterior spinal roots has usually failed to relieve these conditions. This has likewise been the unfortunate experience in cases of painful paralysis of the arm resulting from carcinoma of the breast invading the brachial plexus or from carcinoma of the apex of the lung with regional nerve involvement and in cases of the lightning pains of tabes. Similar pathologic conditions which give rise to pain in the trunk or lower extremity, however, are amenable to chordotomy. Unfortunately, when pain spreads into the shoulder and neck the spinothalamic tract cannot often be divided high enough in the cord to interrupt its fibers to the upper cervical dermatomes. But if the tract is sectioned in the medulla as described, the sensation of pain can be abolished as high as the first cervical segment. In addition, when a useful arm can be preserved its function is but little impaired by the loss of pain and temperature sensation, while it is rendered practically useless by the total anesthesia which follows cutting the sensory spinal roots.

CONCLUSIONS

Experience with the case described in this paper and the cases which have been reported by Schwartz and O'Leary indicates that section of the spinothalamic tract high enough to produce hemianalgesia to the first cervical segment is a practical operation. The lateral wall of the medulla can be easily reached through unilateral removal of the occipital bone down to the foramen magnum. At this level the spinothalamic tract lies between the vagal rootlets emerging from the posterior lateral sulcus and the inferior olive. The posterior inferior cerebellar and vertebral arteries require most careful manipulation. From a limited experience it would seem as though the technical hazards involved in this operation will depend on the difficulty encountered in dealing with these structures. If the vascular arrangement in this single case is typical, the operation will be practical for the average patient, although not too easy. The landmarks for sectioning the spinothalamic tract are just as clearcut in the medulla as in the spinal cord, and the risk of injury to the pyramidal tract is less than in the well standardized spinal procedure. It must be recorded that in this patient after long survival there still remains a troublesome cerebellar ataxia. In future tractotomies of this type the incision in the medulla must be made at a more caudal level in order to avoid damage to the nerve fibers and blood supply of the restiform body.

NOTE.—After this article was written a similar operation was performed by Dr. Donald Munro, of the Boston City Hospital. His patient, a middle-aged man, had metastatic carcinoma of the neck with intractable pain in the neck, shoulder and arm. For this, section of the posterior

roots of the cervical nerves had been performed. This operation, as is so often the case, had failed to relieve his pain. Dr. Munro sectioned the spinothalamic tract in the medulla in February 1941, using the exact technic described in this article. The patient made an uneventful convalescence without the development of any complicating cerebellar ataxia. At the end of four months he remained completely free of his pain and was not taking any narcotic medication.

REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES
FRANK HINMAN, M.D.
SAN FRANCISCO
ALEXANDER von LICHTENBERG, M.D.
MEXICO, MEXICO
ALEXANDER B. HEPLER, M.D.
SEATTLE
ROBERT GUTIERREZ, M.D.
NEW YORK
GERSHOM J. THOMPSON, M.D.
AND
JAMES T. PRIESTLEY, M.D.
ROCHESTER, MINN.
EGON WILDBOLZ, M.D.
BERNE, SWITZERLAND
AND
VINCENT J. O'CONOR, M.D.
CHICAGO

KIDNEY

Tumor.—Gillies [1] studied 50 cases of verified malignant tumor of the kidney in adults.

Tumors primary in the renal pelvis were found in 10 per cent of the cases. In this group intermittent hematuria was the first symptom in each case. Accompanying stones were present in only 1 case.

With small and moderate-sized tumors, pyelograms show irregular filling defects without distortion of the renal outline.

Large tumors invading the kidney cannot be distinguished from primary tumors of the kidney invading the renal pelvis.

Malignant tumors primary in the kidney were present in 90 per cent of the cases of this series. These occurred in men nearly three times as frequently as in women.

In plain roentgenograms, changes in size, shape and density of the kidney, as well as calcium deposits, which occurred in 38 per cent of the cases in which roentgenograms of the kidney were made, should be looked for.

1. Gillies, C. L.: Malignant Tumors of the Kidney in Adults, Am. J. Roentgenol. **43**:629-635 (May) 1940.

Retrograde pyelograms in the presence of tumor show most frequently elongation and compression of one or more of the major calices. Less commonly, there may be complete loss of the normal pelvic landmarks, and rarely, dilatation of the pelvis accompanied with elongation and dilatation of the calices without remarkable compression.

Elward and Spire [2] reported a case of bilateral hypernephroma. In this case there were no subjective symptoms referable to the genitourinary tract. The disease metastasized early to the mediastinum, where all the symptoms seemed to originate. The metastatic growths responded rapidly to roentgen therapy and almost as rapidly became radioresistant. The outcome was fatal. The possibility of cancer of a so-called renal rest of the medastinum with metastasis to both kidneys must be considered.

Hayward [3] reported a case of malignant papillary cystadenoma. The tumor produced no symptoms; in spite of its enormous size the patient did not know of its presence. It had been present for a long period and was of low malignancy. It was discovered during a physical examination made for an acute cardiac condition of which the patient died within twenty-four hours of his admission to the hospital. The tumor apparently had nothing to do with his death. Permission for a complete postmortem examination was refused; so the presence or absence of metastatic growths could not be determined.

Kretschmer,[4] in a discussion of adenomyosarcoma of the kidney (Wilms tumor), stated that although a few cases have been reported in which the tumor occurred in an adult, the fact remains that it is essentially a disease of infancy and childhood. As a rule it runs a silent and rapid course, as is evidenced by the fact that it reaches a large size before medical aid is sought. The histologic picture is unique. The outcome is generally fatal. A multiplicity of theories has been advanced from time to time regarding the pathogenesis.

The sex incidence is of little aid in the diagnosis. In Kretschmer's previous studies 18 patients were boys and 6 were girls. In the 3 cases that form the basis of this paper all the patients were boys. It would appear, therefore, that boys (77.77 per cent) are more frequently afflicted than are girls.

The Wilms tumor is predominantly unilateral. Bilateral tumors have been reported, but they are uncommon. Kretschmer had observed

2. Elward, J. F., and Spire, R. L.: Bilateral Hypernephroma, Radiology **35**:274-281 (Sept.) 1940.

3. Hayward, W. G.: Malignant Papillary Cystadenoma of the Kidney: Case Report, J. Urol. **44**:259-263 (Sept.) 1940.

4. Kretschmer, H. L.: Adenomyosarcoma of the Kidney (Wilms Tumor): Report of Three Cases, Arch. Surg. **41**:379-384 (Aug.) 1940.

2 such growths. The tumor varies greatly in size. The smallest tumor seen by Kretschmer weighed 235 Gm. The growth may nearly fill the abdomen and extend into the pelvis so that it can be felt on rectal examination. This occurred in 2 of the 3 cases reported in this paper. There may be displacement of viscera. The tumor may take its origin from either the upper or the lower pole or from the middle of the kidney. It is encapsulated; it is globular or oval, and it often appears lobulated. The surface is generally smooth, although a nodule may protrude above it. The kidney is separated from the tumor by a sharp line of demarcation. The kidney is compressed by the growth and suffers from pressure atrophy. The renal pelvis also is compressed, except in the rare instances in which the tumor seems to grow around the pelvis. In Kretschmer's experience the tumor was solid. In none of his cases did it have the appearance of a polycystic kidney, although this appearance has been mentioned in the literature.

That this sort of tumor runs a relatively silent course is unfortunate for the patient, since in many cases treatment is sought too late for surgical relief, as was instanced in 2 of the 3 cases reported in this paper. Another drawback is the fact that symptoms referable to the urinary tract are absent, except possibly in the rare cases in which hematuria is present. Likewise, pain is a relatively uncommon symptom and occurs late in the course of the disease. Anemia and loss of weight are late manifestations.

As a rule the diagnosis presents no difficult problem. The presence of an abdominal tumor which has increased rapidly in size and is hard, sometimes nodular and nearly always painless, coupled with the fact that the commonest abdominal tumor occurring in children is the Wilms tumor, should lead to a tentative diagnosis of that tumor in the case of every child with an abdominal growth. The diagnosis is further strengthened by changes in the pyelogram compatible with tumor. In every case in which a tentative diagnosis of Wilms tumor is made, a plain roentgenogram of the abdomen is taken to rule out stone in the urinary tract. The next step in examination consists of obtaining a set of intravenous urograms. Occasionally there may be complete failure to visualize the renal pelvis on the affected side, although the opposite pelvis is shown as normal. But, on the other hand, the pyelogram is frequently most dependable.

A good many differences of opinion still exist as regards the best form of treatment. McNeill and Chilko,[5] in a survey of 383 cases, found that six types of treatment had been followed: (1) nephrectomy

5. McNeill, W. H., Jr., and Chilko, A. J.: Status of Surgical and Irradiation Treatment of Wilms' Tumor and Report of Two Cases, J. Urol. **39**:287-302 (March) 1938.

alone; (2) the use of serum in conjunction with nephrectomy; (3) roentgen therapy to reduce the size of the tumor and kill the embryonal cells, followed by nephrectomy; (4) roentgen therapy followed by nephrectomy and by another course of roentgen treatment; (5) nephrectomy followed by postoperative roentgen treatment to destroy any residual malignant embryonal cells, and (6) roentgen treatment alone. They reported the case of 1 patient alive and well three years after irradiation.

At the time of Kretschmer's report the routine followed by him and his associates was to give the patient a course of high voltage roentgen therapy followed by nephrectomy, after which another course of high voltage roentgen therapy was carried out. In his experience, not all Wilms tumors are radiosensitive. When the growth is radiosensitive and shows a marked reduction in size, nephrectomy is simplified. With the diminution in size of the tumor, corresponding changes are observed in the pyelogram. Attention was called to this phenomenon in a previous publication.

Awareness that malignant tumors of the kidney are common in animals and that these tumors are closely similar to renal cancers in man led Lucké [6] to carry out experimental studies on a certain type of renal cancer in frogs. This is a typical invasive and metastasizing adenocarcinoma. The mechanics of growth of this cancer have been investigated by transplanting it into the anterior chamber of the eye, where its mode of development has been followed by direct and continued observations with the microscope. It was thus learned that the form of the growing tumor depends on the immediate physical environment and that growth takes place according to well defined structural patterns. This conclusion was supported by study of the characteristics of growth of the tumor in tissue culture.

Lucké also discussed the modifying influence of temperature on the growth of cancer and showed that temperature affects the rate and character of cancerous growth in much the same general way as it affects growth of normal tissues.

It is concluded that cancer obeys the physical laws governing normal growth far more than is commonly supposed; neoplastic growth is certainly not lawless.

Calculus.—Gutierrez [7] stated that the possibility of a silent renal stone too frequently is overlooked by clinicians who are handling anemia

6. Lucké, B.: Physical Factors Influencing the Growth of Cancer: Experimental Studies Based on Renal Adenocarcinoma in Animals, J. Urol. **44**:545-558 (Nov.) 1940.

7. Gutierrez, R.: The Significance of Silent Kidney Stone in Anemia, M. Rec. **152**:288-292 (Oct. 16) 1940.

that proves refractory to the usual modes of treatment. While the extent of "silent" renal derangements is well understood by the urologist, it is unfortunate that the internist does not always bear equally in mind, when he is consulted by an anemic patient, that an infected stone in the kidney or in the ureter may run a long silent course and cause marked secondary anemia without producing any urinary symptoms whatever. When simple urinalysis shows nothing suspicious, it too often is assumed that both kidneys are in good condition and that the cause of the anemia does not lie within the urinary tract.

Urologic experience proves, however, that there are many types of renal pathologic processes that do not for a long time reveal their presence through simple urinalysis. Several types of silent renal stone associated with anemia can be readily recognized.

Patients carrying silent renal stones must receive suitable operative intervention, which demonstrates the effect of removal of stone on the general health. Patients who have infected renal stones are carrying a latent focus of infection and are suffering from the effects of general toxemia and septic absorption, which in the course of time will affect the hemopoietic organs and betray itself as stubborn anemia. The renal stone may remain silent for a long time, during which it produces constitutional symptoms long before any local symptoms within the urinary tract betray its presence.

It is obvious that if a stone is impacted painlessly within a ureter or a renal pelvis in such a way as to block completely the escape of urine on one side, all the urine obtained comes from the kidney of the opposite side, which may be sound. In a case of this kind the results of urinalysis are indecisive. Nonopaque stones that do not appear in the plain roentgenogram may be revealed by a filling defect in the retrograde pyelogram.

Randall [8] stated that primary renal calculus is only a symptom and always originates as a slow crystallization of urinary salts on a lesion of the renal papilla. He presented evidence that calcium phosphate, calcium oxalate and uric acid crystallization, to form renal calculi, had in each example which he studied been deposited on a plaque of calcium salts deposited in the renal papilla.

Randall expressed the belief that pathologic change in the papilla precedes the development of a primary renal calculus and acts as the initiating lesion on which these urinary salts crystallize.

It is worthy of mention that calculi supposed to be associated with hyperparathyroidism, hypovitaminosis, odd forms of renal infection and nephrocalcinosis belong to a separate and different form of pathologic

8. Randall, A.: Papillary Pathology as a Percursor of Primary Renal Calculus, J. Urol. **44**:580-589 (Nov.) 1940.

alteration of the papilla, associated with tubular inspissation of salts (calcium infarction), and represent the end results of hyperexcretory states.

Rosenow [9] studied the kidneys in 239 consecutive necropsies. The study was limited to examination of the papillae for calcareous deposits and in some instances for the presence of bacteria.

Usually the microscopic appearance of the calcareous plaques was that of an irregular mass of deep purple-staining material lying in the interstitial tissue. If the plaque was near enough to the surface there was some loss of epithelial continuity. At times the plaque was covered with only a thinned-out single layer of epithelium. In some tubules the calcium seemed to be deposited in the epithelial cells. In many cases bits of calcareous material were found in the medulla. Seldom was calcium found in the ureter. There was practically no evidence of active infection in regions near the calcareous deposits. Rosenow expressed the opinion that probably these calcareous plaques do not initiate formation of stone unless they are so situated as to be in communication with the pelvis of the kidney.

In the study for bacteria, organisms were difficult to find, and they were never found except close to regions of calcification. Almost all the organisms discovered were either diplococcic or streptococcic. Although bacteria were observed in close proximity to regions of papillary calcification, there was practically no evidence of active inflammation. The absence of active inflammation should not minimize the importance of discovering bacteria. If calcification is the end result of damage to tissue, one would not expect to find any evidence of active inflammation, such as collections of leukocytes or lymphocytes.

In this study of the kidneys in 239 consecutive necropsies, plaques of calcareous material were found in the renal papillae in 53 (22.2 per cent) of the cases. Calculi were found in 13 (5.4 per cent) of the cases; they were adherent to the papillae in 5 cases. Bacteria were present in 24 (64.9 per cent) of 37 cases in which examination for bacteria was made. Microscopic intramedullary calcification was present in only 4 of 24 control sections of papillae without grossly visible papillary plaques. Age, sex, grade of arteriosclerosis and necropsy diagnosis were not important factors.

Tuberculosis.—Henline [10] presented a résumé of 40 cases in which a diagnosis of bilateral renal tuberculosis had been made.

---

9. Rosenow, E. C., Jr.: Renal Calculi: A Study of Papillary Calcification, J. Urol. **44**:19-28 (July) 1940.

10. Henline, R. B.: Surgery of So-Called Bilateral Renal Tuberculosis, South. M. J. **32**:1185-1199 (Dec.) 1939.

The difficulties of making an accurate diagnosis were stressed. Cystoscopic examination is often difficult or impossible, owing to marked involvement of the bladder. Ureteral catheterization was impossible in 14, or 35 per cent, of the cases.

Tubercle bacilli were found in the vesical urine (by smear or guinea pig inoculation) in 36 of the cases.

To make a diagnosis reliance must be placed on urographic study, assisted occasionally by the finding of tubercle bacilli in the vesical urine.

Examination of 29 kidneys removed at operation and of kidneys removed at necropsy in 4 cases revealed tuberculosis in all.

At the time the résumé was presented, 21 of 29 patients had lived an average of five and four-tenths years after removal of the more infected kidney in the presence of so-called bilateral renal tuberculosis. Seven had died, after living an average of five and fifteen-hundredths years; 1 patient could not be followed.

Eight of 11 patients had lived an average of seven and fifty-six-hundredths years with medical treatment alone. One died two and a half years after treatment was begun, and trace of 2 was lost.

Patients treated by medical means alone manifested as a rule a clinically different type of renal tuberculosis (fibrotic). A few destructive lesions thus treated (rare) had shown no demonstrable progression.

Ten, or 47.6 per cent, of the living patients who had been operated on showed marked improvement in the condition of the bladder or were practically cured after removal of the worse kidney, while 13, or 61.9 per cent, evidenced general improvement. Four, or 50 per cent, of those treated medically alone showed improvement in the condition of the bladder, and 5, or 62.9 per cent, improvement in general health.

In 1 case in which a diagnosis of tuberculosis in the remaining kidney had been made, the patient, a woman, had undergone transplantation of the ureter to the sigmoid flexure of the colon four years prior to Henline's report, with complete relief of intolerable vesical pain.

Prompt removal of an obviously destroyed kidney is justified provided the function of its mate is sufficient, as this is the method of treatment which offers the greatest hope of relief.

Tuberculosis of the urinary tract was a local disease in 25 of the 40 cases, with no evidence of active lesions elsewhere in the body.

So-called autonephrectomies may be closed off from the bladder, but the renal lesion usually remains pathologically active and, being a focus of infection, should be removed.

The hydronephrosis and hydroureter which frequently develop in the better kidney may be the result of primary tuberculosis of the kidney or may be secondary to a ureteral stricture.

Medical care by an experienced internist is indispensable in the postoperative care of bilateral renal tuberculosis as well as in the treatment of patients suffering from bilateral inoperable tuberculosis.

Pyelonephritis.—Mussey and Lovelady [11] stated that acute pyelitis of pregnancy increases the hazards to both the mother and the fetus. If the disease is recognized early and treated promptly, the hazard is lessened.

Among 121 cases of pyelitis the incidence of spontaneous abortion and premature labor was 4.9 per cent; in 7 cases (5.7 per cent) labor was induced, but this procedure was not found to be necessary prior to the period of viability. In 21 per cent of the cases in this series pyelitis first became evident after delivery. This is an incidence of approximately 0.4 per cent of all confinement cases, and it is obvious that pyelitis should be suspected in cases of otherwise undiagnosed postpartum fever. The findings in this series indicate that acute pyelitis of pregnancy is rarely either the indirect or the direct cause of preeclamptic toxemia and eclampsia.

Evidence indicates that in a majority of cases pyelitis will respond promptly to rest in bed, administration of sedatives and forcing of fluids and that when pyelitis of pregnancy is recognized early and treated adequately few patients will require drainage by ureteral catheter for relief. Favorable results have been obtained recently in a few cases by the administration of preparations of mandelic acid or sulfanilamide. Occasionally drainage with the ureteral catheter is of value in treating acute persistent pyelitis of pregnancy in combination with chemotherapy and other measures.

Injuries.—Sargent,[12] in discussing injuries of the kidney, stated that immediate examination of urine, either voided or catheterized, must be made absolutely routine in all cases of accident. Considering the danger that lurks in hemorrhage and particularly the terrible consequences of urinary extravasation when it occurs, altogether too much is at stake to neglect this simple and easy precaution.

Gross hematuria in cases of accidental injury demands absolutely accurate diagnosis. Many times it proves to be of no particular consequence, but many times also it bespeaks an injury of the first magnitude.

Intravenous urographic examination can be fairly useful as a scout procedure in those cases of accident in which injury to the urinary tract

---

11. Mussey, R. D., and Lovelady, S. B.: Pyelitis of Pregnancy and Its Management in One Hundred and Twenty-One Cases, West. J. Surg. **48**:591-596 (Oct.) 1940.

12. Sargent, J. C.: Injuries of the Kidney with Special Reference to Early and Accurate Diagnosis Through Pyelography, J. A. M. A. **115**:822-825 (Sept. 7) 1940.

is suspected. It must be followed by more exact studies, however, unless sharp outline permits quite exact interpretation and even then if substantial injury seems to be present.

Finally, Sargent reiterated that it is only in the retrograde pyelogram that one can find substantial, dependable and consistent help in determining when and when not to operate on a kidney that has been injured.

Henline [13] stated that retrograde pyelographic examination for suspected renal injury, done under sterile precautions, should afford more accurate information regarding the extent of the renal damage. Use of the newer contrast mediums for pyelography, which readily and harmlessly diffuse with the blood, should add no additional hazard to a ruptured kidney. One has no reason to regret the performance of retrograde pyelographic examination in these cases, and in several instances more precise information regarding the condition of the kidney has been obtained than was possible by excretory urographic studies. Too many general physicians rely on the erroneous information often obtained from the latter. However, many such injuries can be diagnosed by excretory urographic studies alone. One should not hesitate to take a retrograde pyelogram in any instance in which the diagnosis and extent of the injury are in doubt or in which the kidney or the renal pelvis is not well outlined by an excretory urogram. A true rupture of the kidney, resulting in gross injury to the pelvis, cortex or capsule represents serious renal damage. The patient should be operated on as soon as the diagnosis is made, provided shock and other injuries will permit. To postpone surgical intervention in the presence of an operable lesion is poor surgical judgment. The literature contains accounts of many such lesions treated conservatively too long, with a subsequent loss of the kidney or even of life. Surgical intervention, if performed early, may preserve a severely damaged kidney. The degree of shock, however, must first be determined, and treatment must be instituted for the control of shock before surgical operation is begun. The most conservative treatment is (*a*) prompt exposure of the kidney, (*b*) repair when possible or (*c*) early nephrectomy. When doubt persists concerning the extent of the renal injury after all available diagnostic procedures have been done, an early exploratory operation is preferable to prolonged expectant treatment.

Cahill [14] stated that renal injuries vary and that they may be only a minor portion of a profound injury. With a penetrating wound of the abdomen the kidney is often not a major part of the picture but is obscured by intestinal or other injuries. In the late war the infrequency

13. Henline, R. B., in discussion on Sargent.[12]

14. Cahill, G. F., in discussion on Sargent.[12]

of renal injury was due to the fact that most of those seriously wounded died on the field. When the kidney is the major site of trauma, there may be many sources. The symptom most frequently seen is hematuria. Cahill sees no objection to the use of an intravenous urogram in such cases. If the patient is in shock, naturally that condition should be relieved by transfusion and other therapeutic aid and the intravenous urogram taken subsequently. The secretion from the uninjured kidney shows that it is present. The injured kidney may or may not secrete. If it secretes well, the injury is probably not severe and expectant treatment is in order. If the kidney does not secrete and an increasing hematoma is present in the flank, then, operation being contemplated, a retrograde pyelogram may be done.

Stirling [15] stated that, in his experience, in the majority of the cases diagnosis of injuries of the kidney can be made by intravenous pyelographic study. He reviewed 34 recent cases in which there was a positive diagnosis in 23, and in only 7 instances was it necessary to take a retrograde pyelogram. He expressed the belief that instrumental pyelographic procedures should be reserved solely for cases in which bleeding continues, with unsatisfactory pyelograms. In the presence of severe contusions the first intravenous pyelogram may be unsatisfactory, whereas if another is taken in from twenty-four to forty-eight hours it frequently will show a good shadow. In a majority of the cases the lesions reported as ruptures of the kidney are only contusions and respond to conservative measures. Stirling's experimental work and clinical studies indicate that in the presence of severe injury to the kidney operative intervention is more likely to give a good result than is the conservative method. Severe injuries of the kidney produce marked vascular damage, which may later cause ischemia of the kidney followed by hypertension. Patients who have renal injuries should be watched for evidence of hypertension. The loss of blood in renal injuries makes anemia an important factor during convalescence. This complication is due not to the simple loss of blood but to the liberation by the injured kidney of some substance capable of causing toxic destruction of red blood cells.

In 3 instances in O'Conor's [16] experience in which a more or less minor injury of the kidney, at least from a clinical point of view at the time of the injury, apparently responded successfully to palliative treatment the patients (against orders) went back to an active life, and all 3 of them returned with massive hemorrhage coming on as long as four weeks after their discharge from the hospital, which necessitated surgical intervention. One of these patients, who had a massive hemorrhage

15. Stirling, W. C., in discussion on Sargent.[12]
16. O'Conor, V. J., in discussion on Sargent.[12]

which lasted only twenty-four hours, responded quickly to four or five days of rest in bed, left the hospital against orders on the tenth day and returned three and a half weeks later with a kidney which was completely broken in two as the result of lifting a heavy suitcase. Two boys with football injuries were allowed to return to active life. Both resumed playing football within three weeks, and both returned with massive hemorrhage which necessitated surgical intervention. O'Conor expressed the belief that patients who are treated palliatively should be kept at rest at least for two weeks and that their physical activity should be limited for a minimal period of four to eight weeks.

Aneurysm of the Renal Artery.—Aneurysm of the renal artery is rare. Howard, Suby and Harberson [17] gave a résumé of the subject and reported 1 case of false aneurysm and 2 cases of true aneurysm of the renal artery.

Trauma seems to be the most important single cause of aneurysm of the renal artery. Of the 65 cases reported in the medical literature, in 24 there was a definite history of trauma, varying from that received in a very slight fall to a severe crushing injury. The extent of the damage to the renal vessel may be so great that an aneurysm is formed immediately, or it may be slight, with only a weakness produced in the vessel wall, so that the aneurysm may develop slowly over a period of months. Aside from trauma, severe infection seems to be the most important cause of renal aneurysm. Diseases of the arterial wall itself are statistically the third most important cause of renal aneurysm.

The pathologic development of aneurysm of the renal artery is essentially the same as that of any other aneurysm. An aneurysm may be either true or false. By definition a true aneurysm is one whose sac is formed by the arterial wall, one part of which, at least, must be intact. A false aneurysm, on the other hand, is one which follows trauma with rupture of all the coats of the artery and retention of blood by the surrounding tissue. A true aneurysm is usually the result of fatty degeneration, sclerosis, inflammatory changes or degeneration of the elastic fibers of the blood vessel wall. False aneurysms of the renal artery are usually much larger than true aneurysms and as a rule contain laminated blood clot.

A patient may have no symptoms and still have an aneurysm of the renal artery. In cases of the recognized condition, however, those in which the aneurysms ruptured or are relatively large, pain is the most common symptom. With a ruptured aneurysm the pain may be sharp and excruciating, and it is often accompanied with the symptoms and signs of profound shock. The patient who has a large unruptured

17. Howard, H. H.; Suby, H. I., and Harberson, J. C.: Aneurysm of the Renal Artery, J. Urol. **45**:41-54 (Jan.) 1941.

or quiescent false aneurysm may complain of a dull ache in the renal region or may have attacks of renal colic.

Immediate surgical intervention, with nephrectomy as the operation of choice, should be done in all cases of aneurysm of the renal artery. Of the 24 patients who were operated on, only 5 died, a mortality rate of 21 per cent. Three of these operative deaths occurred in cases in which either incision and drainage or partial incision of the sac, not nephrectomy, was done. Subsequent hemorrhage was the cause of death. All of the patients who were not operated on died.

URETER

Anomaly.—Harrill [18] reported a case of hydronephrosis produced by obstruction to a ureter which passed around the right branch of a double vena cava. This was the fifth such case in the literature. After the lower portion of the pelvis had been cut across, the ureter was drawn from behind the right vena cava, placed in the normal position and anastomosed at the point of division. This case is the only one of the kind in which the division and the anastomosis were above the ureteropelvic juncture.

Tumor.—Cook and Counseller [19] stated that, although primary epithelioma of the ureter is a comparatively rare disease, its incidence is sufficient to make it a possible cause of hydronephrosis, especially if it is associated with hematuria. Hematuria is the outstanding symptom, and the blood in the urine is often bright red.

Excretory urograms are valuable if the kidney is still functioning, in that they reveal the extent of the pyelectasis, caliectasis and ureterectasis present, but they may or may not identify the obstructing lesion of the ureter. Retrograde pyelograms are essential to demonstrate the lesion in most instances and should be made whenever a patient with hydronephrosis is of the "cancer age" if the cause is not definitely understood.

Treatment of the condition is surgical, and surgical intervention should be instituted early. Complete extirpation of the kidney, the ureter and the ureterovesical segment of the bladder should be done because of the tendency for the growth to extend through the wall of the ureter to adjacent structures, and all periureteral adipose tissue should be removed with the ureter.

The results of surgical treatment parallel closely the completeness of the operation, the degree of malignancy present and the operability of

---

18. Harrill, H. C.: Rectocaval Ureter: Report of a Case with Operative Correction of the Defect, J. Urol. **44**:450-457 (Oct.) 1940.

19. Cook, E. N., and Counsellor, V. S.: Primary Epithelioma of the Ureter, J. A. M. A. **116**:122-126 (Jan. 11) 1941.

the lesion. Large lesions of low malignancy may be as great a hazard to the life of the patient as small, highly malignant lesions. Roentgen therapy should be administered postoperatively to all patients.

Injury.—Hepler [20] discussed injuries to the ureter which occur accidentally in the course of pelvic operations and therefore are primarily the problem of the general surgeon. Seven hundred and seventy-six such injuries were reported; 659 patients suffered injuries to one ureter, and 117, to both ureters. Hepler added 6 cases, in 5 of which injury was unilateral and in 1 of which it was bilateral. These figures do not represent the frequency with which these injuries occur, because many are unrecognized and some are not reported.

There is lack of uniformity of opinion as to the best methods of treatment, because the numerous contingencies do not permit a categoric plan of management. Certain principles, however, can be laid down, based on the time element, the type and extent of injury and the condition of the patient. When the injury is recognized immediately the problem is largely surgical, but when it is not discovered until after the operation it becomes strictly urologic because of the complications of infection, obstruction and functional damage.

The types of injury, in order of their frequency are those due to ligation, those due to clamping, those due to incision (partial or complete) and those due to resection. Clamping usually destroys the vitality of the crushed segment and is followed by necrosis, so that the badly crushed ureter should be treated as if it were severed. When the injury is discovered during the operation, the ideal procedure for the badly crushed or severed ureter is an end to end anastomosis over an indwelling ureteral catheter. The most important step in this procedure is deviation of the urine by another catheter, inserted in a slit in the ureter well above the line of suture and brought out through the flank. Both catheters are removed in a week. If the injury is near the bladder, a ureteroureteral anastomosis may not be possible, and it may become necessary to implant the proximal end into the bladder.

If a fairly large segment of the ureter has been excised, neither ureteroureterostomy nor ureterocystostomy is feasible, because of the gap in ureteral continuity. The procedures in such a situation, in the order of frequency with which they are recommended in the literature, are: (1) ligation of the proximal end of the ureter and replacement of it; (2) nephrectomy; (3) implantation into the skin (dermatoureterotresis), and (4) implantation into the bowel (ureteroenterostomy).

Hepler expressed the opinion that this order is inverse to the desirability of the operations. The procedure which most frequently is

20. Hepler, A. B.: Management of Surgical Injuries to the Ureter, West. J. Surg. **48**:486-492 (Aug.) 1940.

recommended, to ligate the proximal end of the ureter and drop it back, is not surgical. First, the condition of the other kidney is not known as a rule, and under these circumstances it is unwise to destroy the function of one kidney. Palpation of the opposite kidney gives no information as to its function. Second, ligation of the ureter is followed by hydronephrosis in the great majority of instances and not by primary renal atrophy as is often assumed. Third, this procedure may be an easy way out of the difficulty, but it is not a safe one. Three per cent of the patients will die, 15 per cent will require early nephrectomy for infection, and 24 per cent will have fistulas subsequently.

Immediate nephrectomy will obviate these complications, but the addition of a second major operation, which sacrifices a good kidney, seems a cumbersome way out of the difficulty when a simpler procedure, ureterointestinal implantation, gives a reasonable assurance of renal conservation.

Conservative surgeons may temporize by transplanting the proximal end of the ureter into the skin, but obstruction and infection are so common that delayed anastomoses are difficult and unsatisfactory, and nephrectomy is usually inevitable.

When there is more general recognition of its simplicity and of the absence of postoperative morbidity, ureterointestinal implantation will be decidedly preferred to the other methods of disposal of the injured ureter when a portion of it has been excised.

The management becomes more complicated when the injuries are not recognized until after operation. The symptoms may be interpreted as infection, peritonitis or intestinal obstruction until leakage of urine through the wound or the vagina makes the condition evident. If the ureter has been ligated, hydronephrosis may develop and be unnoticed until months later or until the kidney becomes infected.

If unilateral injuries are recognized soon after operation there are three indications for intervention: (1) drainage of accumulated urine in the flank or pelvis; (2) high lumbar ureterostomy or nephrectomy, if the ureter has been ligated, to provide drainage until it is determined whether or not the suture will absorb, and (3) if a fistula has been established, the use of an indwelling ureteral catheter.

With these exceptions there is no need for haste. Some fistulas will close spontaneously, although too often the so-called spontaneous cure is the result of cessation of function of the corresponding kidney. In the presence of a sound kidney on the opposite side, nephrectomy is the quickest and safest way to relieve the patient of his difficulty. Conservative surgical procedure is apt to fail, because anastomosis of ureters which have been obstructed and infected is an entirely different matter from anastomosis of normal ureters at the time of injury. However, if

the opposite kidney is not sound, some form of anastomosis is necessary —ureteroureteral, ureterovesical or ureterointestinal.

The necessity for immediate treatment in the presence of bilateral ligation is obvious. Reopening the abdomen in an attempt at deligation is to be condemned. The anatomic distortion, the extensive exudate and the inevitable bleeding make this procedure extremely difficult and dangerous for a patient already desperately ill. In a reported series of 13 cases of bilateral ligation of the ureter, immediate laparotomy and deligation were done in 8. Seven of the patients died, and the other later required nephrectomy.

The operation of choice is bilateral high lumbar ureterostomy with the insertion of soft rubber catheters into the pelvis for drainage until it is definitely determined that the ligation will not reabsorb and that the ureteral lumen will not be reestablished. It is then necessary to make some form of ureteral anastomosis. The technical difficulties are increased by the changes in the ureters, which are usually dilated, infiltrated and buried in scar tissue behind thickened peritoneum in a pelvis filled with adhesions. Of the methods of disposal, transplantation to the bowel is the best.

Rusche and Bacon [21] stated that intraureteral instrumentation as a cause of ureteral injury is dependent usually on impaction of a calculus and adjacent disease of the ureter. They expressed the opinion that the present increase in incidence of ureteral perforation is related closely to the recent development of many devices designed to remove calculi. The treatment of a perforated ureter is usually incision and drainage of the extravasated urine and removal of the calculus. Rusche and Bacon reported 14 cases of ureteral injury and 2 cases of foreign body in the ureter in which the lesions and the foreign bodies were due to use of the cystoscope.

Swan [22] considered injuries of the kidneys under three headings: (1) subparietal injuries with no open wound communicating with the exterior; (2) incised and punctured wounds, and (3) gunshot wounds.

Only injuries in the first group are discussed here. These constitute by far the largest group of renal injuries, and the diagnosis is generally easy. The history of injury from a crush followed immediately by pain in the side, collapse and shock, the palpation of a tumor in the lumbar region and the presence of blood in the first specimen of urine passed after the accident usually point to the diagnosis. In cases in which

21. Rusche, C. F., and Bacon, S. K.: Injury of the Ureter Due to Cystoscopic Intraureteral Instrumentation: Report of Sixteen Cases, J. Urol. **44**:777-793 (Dec.) 1940.

22. Swan, R. H. J.: Injuries of the Kidney, Brit. J. Urol. **12**:161-176 (Sept.) 1940.

hematuria is absent the diagnosis can be made on the nature of the accident, the rigidity of the abdominal muscles on the affected side, the presence of a tumor in the lumbar region and the degree of shock. Frequently there is associated rupture of the spleen; in such circumstances surgical treatment should be addressed first to the spleen as the organ less able to suffer delay in treatment.

In a general way it is easier to make a diagnosis of trauma to a kidney than to foretell the amount of damage the organ has sustained. The extent of the perinephric swelling points to the severity of the lesion, but palpation of the mass may be difficult, for the swelling may be masked by the muscular rigidity or the abdominal distention.

The primary treatment consists of rest, warmth and measures to combat the shock. When hemorrhage is still going on, a progressive increase in the pulse rate, increasing anemia and a coincident fall in the blood pressure form important indications for operative intervention. Many patients are too acutely ill to undergo instrumental and roentgen examination, and, in addition, the evidence obtained by these diagnostic aids is often too uncertain to be of great value. An intravenous pyelogram is of use, however, in revealing the presence of a functioning kidney on the other side. Ascending pyelograms may show a more definite shadow, but there remains the risk of injecting the solution into the perinephric effusion or of starting further bleeding.

The actual operation carried out on the kidney must necessarily first be an exploration, and it must be left to the surgeon's judgment to deal with the condition he finds. It should be his constant aim to preserve the kidney if there is any possibility of doing so, and it has been shown that functional recovery is possible after the repair of lacerations at the expense of cicatrizations in the area of injury. Frequently a laceration of the cortical area, even one implicating the calices, may be closed by mattress sutures or by incorporating a piece of muscle or fat in the line of suture to strengthen it. In many cases in which the renal vessels are torn or in which the pelvis is extensively lacerated, nephrectomy must be performed as a life-saving measure. Until the renal pedicle can be controlled, difficulties may arise during the operation from the amount of blood constantly welling up from the depth of the wound, and hemorrhage may be started anew by the manipulations necessary to expose the kidney. Provisions for an immediate transfusion at the close of operation should always be made.

In some cases operation may become necessary at a later stage on account of recurrent bleeding or on account of infection in the area of subcapsular laceration forming localized abscess or pyonephrosis. Infection is more likely to arise, however, in a perinephric effusion (in about 10 per cent of cases) at varying intervals after a renal laceration. It is

evidenced by increase of lumbar pain and tenderness, progressive leukocytosis and irregular pyrexia with pallor and sweating. Later results that may call for operative treatment are those due to contracting scar tissue, which may cause dilatation of one or more calices, or to such cicatrizations about the ureter as give rise to definite hydronephrosis.

Stenosis.—Jewett,[23] from a study of 71 cases of hydronephrosis, established three fundamental causes of obstruction at the upper end of the ureter: bands and kinks, in 4 cases (5.6 per cent); accessory renal vessels, in 24 cases (33.8 per cent), and stenosis, in 43 cases (60.5 per cent). In the group of cases in which stenosis was the underlying cause of obstruction, secondary accelerating factors were accessory renal vessels, infection, kink and fixation, high ureteral insertion and, possibly, rapid renal growth during puberty.

In the majority of normal persons there is no line of demarcation between the renal pelvis and the ureter. Any deviation from the normal funnel-shaped pyeloureteral outlet is probably pathologic. Moderate deviation, sufficient to cause only minimal obstruction, can be compensated for by work hypertrophy of the pelvic musculature.

When the ureter is normal, a sharply defined and permanently persistent ureteropelvic juncture in the presence of pyelectasis should be considered obstructive.

Lymph Channels.—Parker,[24] after making more than one hundred separate injections into various portions of the walls of ureters, stated that no complete network of lymphatic channels can be demonstrated throughout the walls of ureters by means of Gerota's injection mass. The lymphatic capillaries in the walls of the ureters give rise to lymph collectors which pass diagonally outward, through the musculature of the ureters.

These lymph collectors course in the adventitial coverings of the ureters. They may pass upward and downward from the point of injection for greater or lesser distances. Eventually they always leave the renal ducts to pass to regional lymph nodes.

The regional lymph nodes of the ureters belong to the lateral abdominal lymphatic chains, the common iliac, the external iliac and the hypogastric groups of nodes. Lymph nodules located along the lymph collectors from the kidney receive lymph vessels directly from the pelves of the kidneys. Except for these, no lymph nodes separate from the main

23. Jewett, H. J.: Stenosis of the Ureteropelvic Juncture: Congenital and Acquired, J. Urol. **44**:247-258 (Sept.) 1940.

24. Parker, A. E.: Lymph Collectors from the Ureters, Their Regional Nodes and Relations to Posterior Abdominal Lymph Channels, J. Urol. **43**:811-830 (June) 1940.

posterior abdominal and pelvic lymph nodes were found to act as regional nodes for lymph collectors from the renal ducts.

Transplantation.—Hepler [25] reported on the end results of ureterointestinal implantation. The operation of vesical exclusion by transplantation of the ureter to the sigmoid or to the rectum was performed in 27 cases, with 2 deaths, a mortality rate of 7.4 per cent.

When the operation is done for the congenital deformities seen in children, such as exstrophy and epispadias without a vesical sphincter, the results, both immediate and late, are excellent. There were 16 patients in this group, with no postoperative deaths. All of the children except 2 are living and well.

When ureterointestinal implantation is done for the acquired lesions of adults, such as carcinoma of the bladder, intractable tuberculous or interstitial cystitis or inoperable fistula, the damage to the upper part of the urinary tract secondary to these conditions adds to the operative risk and modifies the functional results. There were 11 cases in this group, with 2 postoperative deaths, a mortality rate of 18.3 per cent. There were 4 late deaths, all but 1 of which were from extension of the primary disease and could not be attributed to the ureteroenterostomy. The use of this operation earlier than it ordinarily is employed would make it a truly conservative procedure and not a last desperate means to relieve intolerable symptoms of vesical disease.

One of the chief considerations in bringing about a successful outcome is to avoid obstruction of the ureter at the site of the anastomosis, and to this end the simple methods, which avoid a too tight fixation of the ureter in the submucosal gutter, seem to be the best. Many of the elaborate methods devised to avoid complications seem only to invite them.

In the presence of lesions of the upper portion of the urinary tract the diseased and abnormal ureters add to the technical difficulties and increase the risk of implantation. However, in some situations in which relief is imperative one should not be too easily sidetracked from a contemplated ureteroenterostomy by the dogma that abnormal or dilated ureters should never be transplanted. It is surprising at times what good results are obtained under adverse circumstances.

BLADDER

Diverticulum.—In a review of his 236 cases of diverticulum of the bladder, Kretschmer [26] noted that obstruction at the vesical outlet was

25. Hepler, A. B.: The End Results of Uretero-Intestinal Implantation, J. Urol. **44**:794-807 (Dec.) 1940.

26. Kretschmer, H. L.: Diverticula of the Urinary Bladder, Surg., Gynec. & Obst. **71**:491-503 (Oct.) 1940.

present in all (230) in which data were available (100 per cent). Benign prostatic hypertrophy was present in 153 cases (66.52 per cent), median bar in 34 (14.78 per cent), contracted internal urethral orifice in 18 (7.39 per cent), stricture of the urethra in 5 (2.19 per cent) and congenital valves of the posterior urethra in 3 (1.30 per cent).

Diverticula are rare in women and in children. Eighty-seven per cent occur in the age period after 50 years, a time when obstruction at the vesical neck is common. Seven of the patients in Kretschmer's series were women; in 4 of these the diverticulum was associated with contraction of the vesical outlet, and in 3, with extensive carcinoma of the bladder.

Diverticula may be single or multiple. The incidence in the cases in this series was: single, 137, and multiple, 99. They may vary widely in size, from those with a capacity of a few cubic centimeters to those holding several liters. Some may empty with the contraction of the bladder; others do not and are known as "retention diverticula." This point may be determined by cystograms taken after injection of a contrast medium.

Infection, or diverticulitis, is the most common complication. Once started, it is difficult to treat and leads to peridiverticulitis with adhesions to surrounding structures.

Primary carcinoma arising in a diverticulum is a rare complication. It occurred 4 times in this series. Such a tumor must be distinguished from one which arises in the bladder and invades the diverticulum secondarily.

It is not surprising that stones should occasionally be found in diverticula, because two conditions that predispose to calculosis, namely, retention of urine and infection frequently are present. Stones in diverticula were found in 8 of Kretschmer's cases. Tuberculosis and leukoplakia are rare complications, but they have been reported.

There are no symptoms pathognomonic of diverticulum. The clinical picture is that of obstruction of the vesical neck, and it is usually during the investigation of this condition that the diverticulum is found. Routine cystographic procedures often will reveal the presence of a diverticulum when it is least expected. Lateral as well as anteroposterior films should be made. Contrast cystograms are of value, especially in determining whether the diverticulum empties.

The treatment consists first in removal of the obstruction at the vesical outlet. Whether or not diverticulectomy is performed depends on the size of the diverticulum, its ability to drain and the persistence of residual urine or of infection with dysuria. Kretschmer stated that he does not remove a small diverticulum if the removal of the obstruction relieves the infection and the subjective symptoms. The same rule applies to a

larger diverticulum unless it is close to or impinges on a ureter and produces ureteral obstruction. Under these circumstances Kretschmer removes the large diverticulum first and then disposes of the obstruction of the vesical neck.

De Illyés [27] reported his technic, used for the last twenty years in the University Clinic of Urology in Budapest, Hungary, in surgical treatment of diverticulum of the bladder. A high incision is made into the bladder, the pouch is irrigated, and a long metal instrument resembling an elevator is passed into the pouch. With the sides of the incision held tense by forceps, the wall of the bladder on the side of the diverticulum is freed, mostly by blunt but in part by sharp dissection. It is usually necessary to open the peritoneum horizontally if exposure of the top wall of the bladder is desired. Exposure of the bladder requires the ligation of only a few blood vessels. The wall is cut with straight scissors all the way to the opening of the diverticulum. The opening of the pouch then is encircled with an incision through the entire thickness of the wall. The surgeon proceeding with caution, a layer is reached that separates easily, and the diverticulum can be readily isolated from the bladder. The extremity of the metal instrument, previously passed into the pouch, can be easily felt, and it serves as a guide to the depth of the pouch. This method also facilitates the locating or saving of the neighboring ureter or vas deferens. Furthermore, it enables the surgeon to ascertain whether or not the fundus is separable from the rectum; when the fundus cannot be freed it is wise to make a circular incision around the adhering part to avoid injury to the rectum. This part is left intact, and only the infected mucous membrane is removed.

Since the infected bladder and diverticulum unavoidably come into contact with the edges of the incision, arrangements must be made for drainage. Iodoform gauze tampons having proved inefficient, Illyés has devised a special method of drainage, as follows: Feeling for the lower edge of the os pubis, at a point about 1 or 2 fingerbreadths to one side from the middle of the symphysis, he punctures the soft parts with a blunt forceps; then, feeling the end of the instrument through the perineum, he performs an incision in the skin the size of a buttonhole, through which he thrusts the instrument. A suitable drainage tube is applied and drawn into the wound behind the bladder by means of the instrument. This method of drainage has been of great help in numerous cases. When there is no longer the need for draining, the tube can be taken out; the channel (3 to 4 mm. in diameter) left by it contracts within a few days and closes without leaving the slightest trace.

---

27. de Illyés, G.: The Surgical Treatment of Diverticula of the Bladder, Brit. J. Urol. **12**:104-120 (June) 1940.

This operative method undoubtedly is not perfect, but it is palliative when a radical operation is contraindicated. In cases of older patients who have prostatic hypertrophy and difficulty in emptying the bladder, such diverticula are often present. These patients are already suffering from infection when seen, because urinary obstructions have been treated by catheterization. In such cases Illyés made it a practice first to perform prostatectomy and then to extirpate the diverticulum all in one sitting, as a simpler and more sparing procedure for the patient. At the time of this report he had used this method in 25 cases; in 20 of these healing took place and the patients were healthy. In 11 cases he had performed implantation of the ureter after excision of the diverticulum. In the 168 cases of diverticulum which he had handled, 166 of the patients were men and 2 were women. In the cases of 59 men his treatment was surgical. Illyés expressed his conviction that the diverticulum must be treated surgically, as the only way in which certain and lasting healing can be obtained. The operation is done under sacral anesthesia and local infiltration. All tearing, jerking, undue torsion and rough retraction are forbidden. If this rule is followed, the patient is spared a great deal of pain. Illyés attributed much of his success with serious and complicated conditions to the employment of perineal drainage. He had not seen a single gross infection develop.

Vesicoappendical Fistula.—Pemberton, Pool and Miller [28] considered the rare condition of vesicoappendical fistula and described 3 cases.

They had observed that there usually is a history of distress, perhaps acute, in one of the lower abdominal quadrants. Simultaneously with this distress, burning and frequency of urination occur. Symptoms referable to the urinary bladder alone may be the presenting complaint. From the diagnostic standpoint a history of passage of gas and feces through the urethra is pathognomonic of a vesicoenteric fistula. Cystoscopic examination reveals the opening usually present on the right side of the bladder. Frequently the aperture may not be seen, for a mass of granulation tissue or a depressed necrotic region in the bladder may be the only evidence that a fistula exists. When suspicion exists that a fistulous tract is present, a lead catheter may be passed gently through the aperture and a substance opaque to the roentgen rays may be injected. Cystograms may be of value, in that the medium may outline the abnormal tract.

Pemberton, Pool and Miller reported that 5 patients with vesicoappendical fistulas had been examined and treated at the Mayo Clinic. Two of the cases had been reported elsewhere by Rankin and Judd.

28. Pemberton, J. deJ.; Pool, T. L., and Miller, J. M.: Vesico-Appendiceal Fistulas, J. Urol. **44**:274-278 (Sept.) 1940.

Three men and 2 women ranging in age from 30 to 54 years comprised the group of patients. Definite acute appendicitis was present in 3 cases. In another case the history was suggestive of acute appendicitis, while the patient in the fifth case gave no such history. Pyuria was present in all the cases. Cystoscopic examinations in 3 cases revealed diffuse inflammatory changes in 2, with the same changes present in the left base of the bladder in 1. In the 2 other cases the observations were limited to the right base of the bladder. In 2 cases cystograms were made; one cystogram did not disclose any abnormality, but the other revealed a sacculated bladder. In 2 cases excretory urographic study did not reveal abnormalities.

The 3 patients newly reported on all underwent surgical operation (appendectomy and closure of the opening into the bladder). Of these 3, 1 succumbed to generalized peritonitis.

The authors recommended culture of the urine and institution of appropriate chemotherapy.

Obstruction of Vesical Neck.—Young [29] stated that chronic inflammatory conditions in the female urethra, especially in the deep portions and at the vesical neck, are common in women. They are accompanied with symptoms that often are referred to regions higher in the urinary tract. In most cases, however, local symptoms are present in the urethra and in the bladder. Chronic inflammatory changes in the mucous membrane, in periurethral structures and particularly in the glands are often present and evinced by swelling, by edema, by cystic and polypoid formations and sometimes by the development of definite bars or contractures of the vesical orifice. For the proper study of these changes an antegrade or fore-oblique telescope or urethroscope is essential. These lesions may often be missed during cystoscopic examination with the right angle telescope. The conditions which produce such severe local and referred symptoms are readily cured by endourethral treatment: applications of silver nitrate fulguration, the punch operation or excision of the obstructing bar. Severely inflamed regions may be treated either with the simple punch instrument or with the electrical resectoscope. Care must be taken not to overdo, lest temporary incontinence occur. Accurate and adequate endoscopic methods often clear up long-standing and troublesome conditions.

Rupture.—Peacock [30] reported a series of 28 cases of rupture of the bladder. The ages of the patients varied from 11 to 70 years, the average being 34 years. Eighteen patients were males and 10 were females.

---

29. Young, H. H.: The Pathology and Treatment of Obstructions at the Vesical Neck in Women, J. A. M. A. **115**:2133-2135 (Dec. 21) 1940.

30. Peacock, A. H.: Rupture of the Urinary Bladder, Northwest Med. **39**:248-252 (July) 1940.

Hazardous occupations, such as logging, railroading, electric work and stevedoring, increase the incidence of rupture of the bladder in men and boys. Loggers comprise 25 per cent of the patients; students, 25 per cent; housewives, riding as automobile passengers, 14 per cent, and laborers, 11 per cent.

The most frequent cause of rupture of the bladder was fracture of the bony pelvis. In 85 per cent of the cases reported by Peacock such fractures were present.

Fifty per cent of ruptures of the bladder were due to motor vehicle collisions and accidents. The average interval between the accident and surgical treatment was eleven hours. Few patients who were allowed to go without operation for several days escaped disastrous consequences. Four deaths occurred in the series.

The commonest complications were pyelonephrosis, perineal abscess from hematoma, peritonitis, osteomyelitis, laceration of the kidney, rupture of the rectum and vesical calculus. The long-standing drainage of the bladder, the infection and the decubitus position are all contributory to slow convalescence.

PROSTATE GLAND

Hypertrophy.—Henline [31] described a method of subtotal perineal prostatectomy. The pathologic changes of prostatic disease frequently are overlooked in selecting the surgical procedure for relief of symptoms. Each of the three main prostatic procedures has its place, and no one method should be used to the exclusion of the others. Infection of the remnants of the functioning prostatic gland, prostatic calculi and early malignant disease, particularly in the posterior lobe of the gland, may be completely removed only by the perineal approach. Patients should be warned of the frequent occurrence of impotence following subtotal perineal prostatectomy. Recent improvements in surgical technic and mastery of procedure should dispel the fear of urinary incontinence or fecal fistula.

Emmett [32] considered the preoperative and postoperative care of patients on whom transurethral prostatectomy is performed. According to him, preoperative care begins with the first visit of the physician when he is called to relieve the patient of retained urine. The important factors to be kept in mind during instrumentation are: that the vesical mucosa has been traumatized by stretching, which makes it more susceptible to infection; that urinary retention of long standing produces

31. Henline, R. B.: Prostatic Disease, with Special Reference to the Various Causes and Types as Well as Their Treatment, South. Surgeon **9**:360-368 (May) 1940.

32. Emmett, J. L.: Preoperative and Postoperative Care in Transurethral Prostatectomy, S. Clin. North America **20**:1061-1075 (Aug.) 1940.

stasis and renal insufficiency; that instrumentation may cause exacerbation of an infection already present, and that the physician is dealing with patients of advanced age, whose resistance to any disease is lower than that of younger persons.

The difficulties of catheterization are easily understood when one realizes that at times there is difficulty in catheterizing a normal male urethra. Furthermore, a "pocketed" posterior urethra may add difficulty. Time should always be taken to sterilize catheters properly, and time should also be taken to prepare the patient with opiates prior to catheterization so that he will not be tense and irritable.

The technic of catheterization is as follows: Proceed gently and slowly, using a plain soft rubber catheter. If this instrument cannot be passed, use one with a coudé tip. If this fails, try a filiform followed by a Phillips catheter or a semirigid woven catheter with a coudé or a bicoudé curve. Metal catheters are best avoided, as they may cause more harm than good.

If catheterization is extremely difficult, there are several other procedures that may be tried. Usually after needle aspiration of the urine the catheter may be passed easily. The patient may be hospitalized and anesthetized before catheterization is attempted. Finally, suprapubic cystostomy may be necessary.

Aside from the patient's discomfort from acute urinary retention, the only indication for preoperative drainage of the urinary tract is renal insufficiency. This is in direct contrast to former teaching, which held that preliminary drainage was essential in order to "vaccinate" the patient against his infection. However, infection is an important factor in preliminary drainage, and Emmett pointed out that infection produced by the indwelling catheter is due to poor technic and uncleanliness. The institution of prolonged drainage should begin by introduction of a carefully sterilized catheter with rigid aseptic precautions. The catheter should be carefully adjusted and fastened in place. A self-retaining catheter may be used, but in either event the catheter should be connected to a closed system of drainage. To reduce the incidence of ascending infection, the drainage bottle should be boiled before being replaced after removal for emptying. It is extremely important that the catheter be adjusted immediately if it becomes painful or if the patient voids around it. Unless this is done, chills and fever will result. It is essential that the strips of adhesive tape used to fasten the catheter be placed so that they do not occlude the urethral meatus and prevent free drainage of the secretions of the urethra.

The only indication for preliminary drainage is a retention of urea in the blood, and if the value for blood urea is more than 50 or 60 mg. per hundred cubic centimeters urethral drainage should be employed. However, this is a variable factor; for instance, in the event that the

concentration of urea is 200 or 300 mg. per hundred cubic centimeters and the urinary output is good (2 or 3 liters daily) while the patient is being prepared, it is considered safe to proceed when the concentration of urea is about 150 mg. per hundred cubic centimeters, for in some cases it may become fixed at a high level. Furthermore, the danger from infection is great enough so that it is felt best to proceed with transurethral resection. Suprapubic drainage is rarely indicated, according to Emmett, for the purpose of preliminary drainage, this procedure being employed in only about 6 cases a year, during which time 1,000 prostatic resections are performed.

Concerning the administration of fluids in cases of renal insufficiency, it is best not to exceed 3,000 cc. daily, and care should be taken not to give too much salt. The associated diseases of which one should be aware are cardiac disease, hypertension, arteriosclerosis, diabetes and senile dementia, as these complicate the management of patients with prostatic obstruction.

The question of the preoperative use of urinary antiseptics is usually not considered unless the urine is very foul, in which case vesical lavage and antiseptics are used. Usually it is best to proceed with resection as soon as possible. Blood transfusions are not given unless the concentration of hemoglobin is less than 10 Gm. per hundred cubic centimeters of blood. Emmett expressed the belief that transfusion is more beneficial after resection.

The postoperative care was summed up under three headings: (1) hemostasis, (2) adequate drainage and (3) prevention and eradication of infection. At the conclusion of resection the usual custom is to insert a no. 22 F. soft rubber urethral catheter, but if there is considerable oozing a hemostatic catheter bag is used and appropriate tension is made by traction. The most important factor in the control of bleeding is irrigation of the bladder. This should be done as often as every twenty or thirty minutes for the first hour or two after operation. In most cases the urine is clear after eighteen to twenty-four hours. Immediately after resection, the important precautions to prevent further hemorrhage are to drain the bladder well and keep the patient quiet. In the event that hemorrhage does occur after resection, it is necessary to evacuate the clots from the bladder, and if doubt exists it is best to reexamine the vesical neck for the presence of bleeding vessels. Blood transfusions should be used, as most deaths from renal insufficiency, oliguria and cardiac failure are due to excessive loss of blood.

Fluids are given postoperatively as follows: From 1,000 to 1,500 cc. of physiologic solution of sodium chloride or a 5 per cent solution of dextrose is given intravenously immediately after the operation; fluids and food are given by mouth on the afternoon of the day of operation.

The catheter is usually left in place for forty-eight or seventy-two hours after resection. If the patient voids well after the catheter is removed, it is not reinserted until the patient has left the hospital; about the tenth day, during a visit to the office, a catheter is passed, and if there is no residual urine the patient is dismissed on the twelfth or fourteenth day after operation. If subsequently the patient experiences any difficulty in voiding, the catheter is reintroduced after about six hours. If there is any residual urine, the catheter is left in for forty-eight hours. If residual urine persists it is best to plan another cystoscopic examination, but this should not be done until seven or eight days after the first operation.

Febrile reactions after a cold punch operation most commonly are due to: (1) infection in the prostatic bed, (2) acute pyelonephritis and (3) septicemia. Administration of mercurochrome intravenously, 5 to 10 cc. of 1 per cent solution in 500 cc. of physiologic solution of sodium chloride, may be a life-saving procedure. When definite septicemia is present, sulfanilamide or one of its derivatives is most efficacious. In the uncomplicated case, the patient is allowed to be up in a chair the day after operation.

Acute epididymitis subsequent to resection is becoming rare, since resections are being done more completely. Postoperative urethral stricture is becoming less common, since surgeons are resorting to perineal transurethral resection when the urethra is too small to admit the resectoscope comfortably. Occasionally a periurethral abscess is encountered; such an abscess should be incised as soon as the diagnosis is made. Postoperative pneumonia is treated in the usual manner. Fortunately perforation of the bladder is becoming rare, since surgeons have become better trained in the technic of transurethral resection. However, if this complication is suspected, suprapubic drainage should be carried out if there are signs of extension or extravasation.

Transurethral Resection.—Kretschmer [33] discussed the present trend of transurethral resection. He stated that shortly after the inauguration of resection the operation was severely criticized because of some of the bad results which followed its use. The method was criticized without taking into consideration the man who sat at the other end of the resectoscope.

Whereas formerly there was much difference of opinion regarding the type of patient who should have a resection, there is one definite common ground on which all urologists agree: Practically all believe that the small bars, contractures, small middle lobes and small intraurethral lobes are best handled by resection, and most urologists agree

33. Kretschmer, H. L.: The Present Trend of Transurethral Resection, J. A. M. A. **115**:89-93 (July 13) 1940.

that the carcinomatous prostate when it produces obstruction should be handled by resection. It goes without saying that resection in a case of cancer of the prostate is much to be preferred to a permanent suprapubic fistula, even if a second and a third resection become necessary. Moreover, many patients afflicted with carcinoma of the prostate are seen so late in the course of the disease that only a small percentage are amenable to radical surgical treatment.

The only debatable point centers around the treatment of the enlarged prostate. Here opinions still differ. Surgically minded physicians have taken a definite stand that a large prostate should be removed by open operation, whereas many urologists believe that even a very large prostate should be resected. Another interesting fact is that as the experience of the operator increases the number of his resections increases and the number of his prostatectomies decreases, which is akin to stating that as the operator's experience increases the number of prostatectomies decreases because increasing proficiency permits him to resect the large prostates.

The question of whether the very large prostate should be treated by resection or by prostatectomy may automatically solve itself in the future, for the patient with prostatism will seek relief early rather than late in the course of the disease, long before the prostate reaches an enormous size and prior to the onset of the severe symptoms which occur late in the course of the disease.

Once he is aware of the fact that he may obtain relief by a method that has in its favor a low mortality rate, a much shorter period of morbidity, fewer and less serious complications and a good functional result, it is reasonable to assume that the patient of the future will seek relief early rather than late in the course of prostatic disease.

In discussing the treatment of diverticulum of the bladder and resection, Kretschmer stated that it is necessary to assume that the obstruction at the vesical neck has been removed completely. He does not remove a small diverticulum if the urine is clear and subjective symptoms are present. With a larger diverticulum, if the obstruction has been completely removed, if the patient is free of symptoms, if the urine is clear or slightly hazy owing to bacteria and contains a few pus cells and if the diverticulum is not close to the ureter so as to produce ureteral obstruction, Kretschmer concluded that administering a urinary antiseptic and keeping the patient under close observation are all that is necessary. However, if the ureter is obstructed, the pyuria does not clear up and there are recurring attacks of chills and fever accompanied with urinary symptoms, or if the diverticulum does not empty, he does a diverticulectomy. With a very large diverticulum, as a rule, he removes the diverticulum first and then performs the resection.

Hemorrhage, which in the early days occurred frequently during resection, has ceased to be much of a problem. A hemorrhage which occurs during the second postoperative week is probably always due to a secondary infection. The treatment has become standardized and consists of evacuation of clots, if present, and visualization and fulguration of the bleeding point or points. At times it may be advisable to resect the bleeding area. If the bleeding cannot be controlled, a Foley bag may be used. In cases of resected carcinoma of the prostate late bleeding is always due to a recurrence of the growth.

During the early period of resection, vasectomy was recommended and used by a large number of urologists as a routine procedure, the object of which was to prevent postresection epididymitis. At present there is a decided trend away from vasectomy as a routine procedure. In Kretschmer's first series of cases vasectomy was not employed; in 12 per cent of this series there was postresection epididymitis. He then employed vasectomy as a routine for several years. He stated that for the past three or four years he has not performed vasectomy except under certain circumstances. In his recent experience postresection epididymitis had been uncommon. He reviewed 250 recent cases taken at random from his records and found that epididymitis had developed in only 5 of them, an incidence of 2 per cent. Vasectomy is employed for patients who come to the hospital with a severe acute attack of epididymitis and are in need of catheter drainage because of complete retention or a large amount of residual urine and infected urine.

Infarction.—Hubly and Thompson [34] stated that infarction of the prostate gland occurs more frequently than has been commonly appreciated. They reported 3 cases illustrative of the gross and microscopic pathologic changes and of the stages through which an infarct passes, namely, from the acute to the healed, or scar, stage. The causative agents were believed to be trauma, adenomatous hyperplasia producing a distortion of the intraglandular vascular supply, prostatitis, arteriosclerosis, thrombophlebitis, circulatory stasis and embolism. They concluded that the symptoms caused by infarction in the prostate gland are mainly mechanical and that they are dependent on relative changes in the volume of the gland, which are in turn dependent on the stage of infarction present. In the early stage, when there is swelling in the involved region, symptoms of urinary obstruction may develop if the infarct is large enough. Later, when the infarct has undergone cicatrization and the prostatic volume has been thereby reduced, the symptoms of urinary obstruction may be relieved. Whether or not relief is obtained

34. Hubly, J. W., and Thompson, G. J.: Infarction of the Prostate and Volumetric Changes Produced by the Lesion: Report of Three Cases, J. Urol. **43**:459-467 (March) 1940.

depends on the size of the infarct as compared with the size of the gland. If the infarct is large, partial prostatectomy may take place automatically.

Carcinoma.—Gutierrez [35] discussed the change in conception of cancer of the prostate and its treatment. Until recently urologists adopted a defeatist attitude and assumed that patients no longer amenable to prostatectomy (which meant the great majority) must face suprapubic cystostomy and with it all the sufferings entailed by a catheter-burdened life. But with the perfecting of the technic of transurethral resection there has been a growing recognition that patients with cancer of the prostate too advanced for radical operation may obtain relief of symptoms by this palliative operation, which not only is simplicity itself in the hands of one experienced in its execution but can be repeated from time to time as the symptoms may require.

With reference to the stage of development of the disease and the mode of treatment, cancers of the prostate may be divided into three groups; group 1 embraces the "silent" cancer, with no symptoms; the patients are amenable to prostatectomy. Group 2 comprises cancers which still are circumscribed within the capsule of the prostate and are still freely movable, though urinary symptoms may have appeared. The patients may also be treated by prostatectomy. Unfortunately, however, these two groups cover only about 10 per cent of cancers, and the remaining 90 per cent fall into group 3, which is made up of carcinomas so far advanced that metastasis has already occurred into the lymphatic and osseous systems when the patients are first seen by the urologist. By this time the patients usually are suffering not only from urinary symptoms but from arthritis, lumbago or some other type of pain due to invasion of nerve sheaths or of bones; in short, with generalized carcinosis. Prostatectomy is then useless, but transurethral resection may well be used for relief of urinary distress.

In view of the great number of cases in which carcinoma of the prostate has already arrived at this inoperable stage before the patient comes for treatment, all men who have reached the age of 50 years should be urged to have routine examinations of the prostate once a year, so that if the least sign of a cancerous nodule is discovered the growth may be totally removed before it becomes inoperable. Since in the early stages of the disease there are no urinary symptoms to bring them to the urologist, it is important that every general practitioner learn the technic of examination of the prostate and emphasize its importance to all elderly men who come for general physical examination. If a nodule is found, a needle biopsy will at once reveal whether or not it is carcinomatous. If the results of biopsy are positive and the roentgen

35. Gutierrez, R.: The Changing Conception of Cancer of the Prostate, Am. J. Surg. **48**:330-341 (May) 1940.

rays show no metastasis, perineal prostatectomy at this early stage in most cases will accomplish complete cure. Such routine examinations would bring into groups 1 and 2 (operable cancer of the prostate) many growths which at present go into group 3 before the condition is recognized.

To the unfortunate patients with cancers in group 3 modern urologic practice brings the almost unfailing assurance that they may still have their urinary symptoms relieved or even wholly abated and their lives prolonged in comfort by undergoing transurethral prostatic resection. The objection traditionally raised against incision of a malignant growth has no weight in this connection, since there is admittedly no hope of cure. Metastatic extension is already present, and its avoidance is no longer a consideration. The patients can thus be saved from a catheter-burdened life, and resection may be repeated from time to time as the need arises. The use of roentgen rays is recommended for relief of pain and also for control of metastasis. About 5 per cent of the patients will not be amenable to transurethral resection, owing to impossibility of passing any kind of instrument into the urethral canal, on which the carcinoma has encroached. For these patients suprapubic drainage or, as an alternative, possible transplantation of the ureters must still remain the only means of relief.

Carcinoma of the prostate is now known to be present in about 20 per cent of all cases of prostatic obstruction and is three times as common as cancer in any other internal organ of the male. Under this new conception of its management the prognosis for a five year cure is greatly improved.

Kickham [36] emphasized several striking features of carcinoma of the prostate. These are: (1) its extremely high incidence, (2) the insidiousness of its onset, (3) the viciousness of its local extension and metastatic dissemination, (4) the deceptiveness of its clinical manifestations, (5) the extreme difficulty of early diagnosis and (6) the utter hopelessness of cure unless the lesion is recognized in the early stages and unless prompt measures directed to complete eradication are adopted in these early stages.

Postmortem examination was carried out in 132 of Kickham's series of carcinomas of the prostate. Analysis revealed that 63 autopsies (54.2 per cent) showed obstructive changes in the upper portion of the urinary tract secondary to direct or indirect ureteral occlusion by malignant growth. The obstruction was bilateral in 47 instances and unilateral in 16. In 58 cases (44 per cent) there was sufficient renal damage from the effects of urinary obstruction and urosepsis to constitute an adequate

36. Kickham, C. J. E.: Diagnostic Pitfalls in Carcinoma of the Prostate, J. Urol. **45**:92-101 (Jan.) 1941.

cause of death. The results of postmortem examination have demonstrated definitely that impairment of renal function is the most common cause of death from carcinoma of the prostate. Metastatic disease in the postmortem studies was found in the regional lymphatics in 73 cases (63 per cent). Other organs involved were the liver, in 27 cases (23 per cent); the lung, in 17 cases (15 per cent), and the kidney, in 7 cases (6 per cent). Involvement of the bladder was recorded in 30 cases (26 per cent) and invasion of the rectum in 12 cases (9 per cent).

Digital examination of the rectum is the "sine qua non" in the establishment of the diagnosis of prostatic cancer. The greatest significance must be attached to hardness of the gland, whether diffuse or localized, as this is suggestive of carcinoma.

Metastasis to bones was demonstrated in 58.7 per cent of cases. In 87 per cent of these metastasis was shown by roentgen rays in the bones of the pelvis. The lumbar portion of the spine was the site of the deposits in 55 per cent.

SURGERY OF THE KIDNEY

Preoperative and Postoperative Care.—Priestley and Schulte [37] considered the subject of preoperative and postoperative care for patients who undergo operations on the kidney. They pointed out that, although this care is similar in many respects to the care of any general surgical patient, there are certain special considerations that should be kept in mind.

The total and the relative function of the two kidneys should be determined as accurately as possible preoperatively. For this purpose the use of excretory urographic study is a great help provided that renal function is within normal limits or only slightly reduced. In the event that there is obstruction, such as that due to a stone impacted at the ureteropelvic juncture, a delayed plain roentgenogram of the urinary tract taken a few hours or even a day after the injection of the medium intravenously may afford the necessary information. In some cases cystoscopic study and catheterization of each kidney may be necessary to determine the information required. In any event, in each case the blood urea should be determined, and in some cases the values for carbon dioxide–combining power, creatinine and blood chlorides should also be determined. An elevation of the concentrations of blood urea and creatinine and a lowered carbon dioxide–combining power will be found in patients with poor renal function. There is almost always associated secondary anemia, and the patient usually is weak and has a poor appetite. Preoperative treatment should include a generous

37. Priestley, J. T., and Schulte, T. L.: Preoperative and Postoperative Care for Patients Who Have Operations on the Kidney, S. Clin. North America **20**: 1049-1059 (Aug.) 1940.

supply of fluid administered intravenously (physiologic solution of sodium chloride and 5 per cent or 10 per cent dextrose alternately). When definite acidosis is present the value of the carbon dioxide–combining power is materially lowered, and it is well to administer 5 per cent solution of sodium bicarbonate intravenously. The amount of sodium bicarbonate necessary may be computed by a mathematical formula; however, it is best never to give more than 500 cc. of 5 per cent solution at any one time.

If severe anemia is present, multiple blood transfusions are of distinct benefit. If serious infection is present, treatment with an appropriate urinary antiseptic may be employed judiciously. But in some cases treatment of this type produces anorexia and nausea, and the ultimate effect on the patient's general condition is detrimental. If there is marked obstruction to one or both kidneys, particularly in the presence of a certain degree of renal insufficiency, drainage with an indwelling ureteral catheter may be beneficial.

In cases of nephrolithiasis it is important to know the size, contour and number of calculi present, as well as their exact location within the kidney. Also, the patient should be investigated to detect any evidence of dietary or vitamin insufficiency, endocrine disturbance or metabolic disorder. The presence or absence of infection should be ascertained by appropriate methods. The concentration of urinary calcium as well as the presence of cystine in the urine should be determined if indicated. The management of the patient with hydronephrosis requires accurate information concerning the relative function of the two kidneys; furthermore, infection, if present, should be reduced to a minimum before operation is considered. Catheterization for uninfected hydronephrosis may be undesirable unless immediate operation is planned.

The anesthesia of choice usually is spinal, induced with procaine hydrochloride; however, if the patient is a good surgical risk, an inhalation anesthetic may be suitable. On the other hand, if he is a poor risk, the use of pentothal sodium with local infiltration at the site of the incision with procaine hydrochloride is employed.

Concerning postoperative considerations, it is well to withhold all orally taken fluids for at least thirty-six to forty-eight hours after operation, and then they may be given in small amounts, such as ½ ounce (15 cc.) of water per hour until the patient demonstrates his ability to tolerate fluid. Such a plan will obviate abdominal distention, which is easier to prevent than to treat. The fluid intake should be about 3,000 to 4,000 cc. daily. If renal function is poor, larger amounts may be necessary. If nephrectomy has been performed it is well to determine the value for blood urea at some time during the early postoperative period.

Drains, usually of the Penrose type, are left in place for at least seven days; if the operative field has been grossly contaminated they are left in place longer. In cases of tuberculosis in which nephrectomy has been performed no drains are used.

The postoperative treatment of patients with renal insufficiency requires care in the prevention of pulmonary edema from intake of too much fluid. This is best done by determining the concentration of blood urea, the carbon dioxide–combining power and the urinary output and balancing these observations against the amount and type of fluid to be used intravenously. Particular attention must be paid to the gastrointestinal tract, as anorexia and nausea are common. Under these circumstances, foods which appeal to the patient are often better tolerated and more valuable than any special diet selected by the physician.

Nephrostomy tubes are connected by a closed aseptic system to a sterile bottle at the side of the bed. Postoperatively the tube should be irrigated with warm boric acid solution often enough to prevent blood clots from forming and plugging the tube. If there is an appreciable amount of infection, lavage with some particular type of solution, such as phosphoric acid (0.25 per cent to 0.5 per cent), acetic acid (1 to 3,000) or potassium permanganate (1 to 8,000), may be employed.

In order to prevent the recurrence of renal calculi it is important that all stones be removed at the time of operation, that any factor which predisposes to obstruction at the ureteropelvic juncture be corrected and that a nephrostomy tube be inserted if it appears desirable. Subsequently, chemical analysis of the stones should be carried out; the amount of calcium in the urine should be determined, and any infection in the urinary tract should be eradicated. Furthermore, distant foci of infection should be cleared up. The patient should be studied for vitamin deficiency, endocrine abnormality and metabolic disorder. Prior to dismissal of the patient a plain roentgenogram should be made in order to make certain that no stones are present. Periodic examinations should be conducted subsequently.

The question of irradiation also was considered by Priestley and Schulte. They expressed the opinion that irradiation is of questionable value preoperatively or postoperatively for patients who have hypernephroma and is of no value in cases of squamous cell epithelioma of the renal pelvis. It appears to be of value both preoperatively and postoperatively in the treatment of children with a Wilms tumor.

Finally, they considered management after plastic operations in cases of hydronephrosis. They expressed the opinion that the ureteral splinting catheter and the nephrostomy tube should be left in place for two to three months after the operation and that it is safer to err by leaving the tubes in too long than by removing them too soon.

TESTIS

Tumor.—Gilbert and Hamilton [38] reviewed more than 7,000 case records of testicular malignant disease in an attempt to define the relation of testicular ectopy to testicular cancer. In 840 of the 7,000 cases of cancer (approximately 11 per cent) the cancer was associated with ectopy. That 11 per cent of all testicular tumors occur in the 0.23 per cent of males who are cryptorchid proves that neoplastic growth occurs more commonly in ectopic than in scrotal testes, about forty-eight times more often than would be expected from chance association.

In 96.8 per cent of cases of unilateral cryptorchidism and one testicular tumor the tumor was in the undescended testis. In 69 cases of bilateral cryptorchidism and cancer of the testes the tumors were bilateral in 24.6 per cent as against a bilaterality of only 0.7 per cent in approximately 6,200 cases in which the tumors occurred in scrotal testes. Thus the condition of the opposite testicle when one is affected by malignant disease in the presence of bilateral cryptorchidism is a matter of grave concern and presents a dilemma similar to that encountered with unilateral ovarian and mammary cancer.

Despite this apparent correlation between testicular ectopy and testicular malignant disease, it is not proved that the ectopy is carcinogenic or that cancer is the result of an abnormal condition in any particular site in which the testicle may be lodged. Also, there is no evidence that any particular site of ectopy or even the condition of ectopy hastens carcinogenesis. The average age at which testicular malignant disease is observed and the relative incidence at various ages are almost identical for abdominal and inguinal testicular ectopy. The average age of appearance is 31 years for scrotal as compared to 34 years for ectopic testes.

Gilbert and Hamilton concluded that the predisposition to cancer of the testicle can be better correlated with congenital conditions as a whole than with an ectopic site alone, which is only one of the congenital anomalies. Congenital hernia and pseudohermaphrodism are common. Of 345 patients who had abdominal testicular tumors, 11 per cent were pseudohermaphrodites. In patients with cancer of the testes congenital defects associated with other than the reproductive organs included such conditions as cleft palate and harelip, but these were not as common as hernia, pseudohermaphrodism and ectopy.

A question often raised as to the management of cryptorchidism is whether or not orchiopexy lowers the incidence of testicular malignant disease. There had been reported 77 cases of malignant disease in which

38. Gilbert, J. B., and Hamilton, J. B.: Studies in Malignant Testis Tumors: III. Incidence and Nature of Tumors in Ectopic Testes, Surg., Gynec. & Obst. **71**:731-743 (Dec.) 1940.

orchiopexy was performed. This number may be said to be relatively few, and the results of orchiopexy have been in the main free from malignant complication. But until more specific data are available there can be no foundation for the assumption that orchiopexy may lower the incidence of malignancy. The rationale for orchiopexy must rest on the placement of testicles where they can be more closely observed, the repair of hernias that commonly accompany cryptorchidism and the encouragement of spermatogenesis and possibly also of increased hormone secretion.

Abdominal placement of testes which were seemingly impossible to put into the scrotum was followed in 14 cases by reports of tumors. Such occurrences in testes resident in the abdomen make surgical judgment in the individual case a choice between the danger of carcinogenesis and the benefits to be obtained from secretion of the testicular hormone; spermatogenesis in abdominal testes can scarcely be expected.

In view of the significance of the correlation between testicular cancer and ectopy, Gilbert and Hamilton [38] made a complete collection of reports on cancer of the testis. Their analysis of 841 cases brings out the following points:

Patients who have cancer of the testis commonly exhibit congenital defects, such as ectopy, hernia and pseudohermaphrodism.

Cancer of the testis is associated with ectopy as follows:

1. In 11 per cent of recorded cases of cancer of the testis there is concomitant ectopy, a correlation forty-eight times higher than would be expected by chance association.

2. Among the patients who have cancer of one testis and unilateral cryptorchidism, 97.5 per cent of the tumors are in the ectopic testis.

3. Of bilaterally cryptorchid men who had cancer of one testis, 24.6 per cent later had a tumor in the second testis, whereas men with both testes in the scrotum subsequently had a tumor in the second testis in but 1 per cent of the cases. The frequency of bilateral involvement of ectopic testes is thirty-two times that of involvement of scrotal testes.

Ectopy is not necessarily the cause of cancer. 1. Cancer appears at an earlier average age in cases of scrotal than in cases of ectopic testes, 31 as compared with 34 years; it does not appear that ectopy hastens carcinogenesis. 2. A tumor occurred in the descended but not in the undescended testis in 23 cases of unilateral cryptorchidism. 3. No particular tumor type is favored by an ectopic site. 4. The predisposition to cancer of the testis can be better correlated with congenital conditions than with an ectopic site.

The incidence of cancer of the testis is highest during the reproductive years, being markedly greater from puberty until about the sixtieth year and reaching a peak in the thirty-fifth to the thirty-ninth year. This

is true not only with regard to the percentage incidence of cancer of the testis in the various age groups but with regard to the number of living males in these age groups. Between the twenty-fifth and the fifty-ninth year the percentage incidence is almost double, and from the thirty-fifth to the thirty-ninth year almost triple that expected by chance visitation in living males.

The undescended testis must be regarded from the viewpoint of potential malignant disease and as an organ unfavorably situated for spermatogenesis but conducive to herniation. Orchidopexy is not the complete answer, for 77 tumors have been observed in testes previously transferred to the scrotum from an ectopic position. The incidence of cancer in the second testis (subsequent to involvement of one testis) is approximately 1 in 100 cases of scrotal testes and almost 1 in 4 in cases of bilateral cryptorchidism. These facts direct attention on the second testis when one testis is known to be malignant and are equivalent to ordering continued observation in patients with ectopy. Even in men who are not cryptorchid the possibility of involvement of the second testis after the occurrence of cancer in one testis is a matter of import, for the frequency of bilateral tumors is some 770 times the incidence of cancer in either testis among the general male population.

Barringer and Earl [39] discussed teratoma testis, giving a survey of 37 postmortem records.

The 37 patients who died of teratoma testis ranged in age between birth (1 was a stillborn infant) and 47 years.

Metastasis may be and generally is both lymph borne and blood borne.

If a left supraclavicular signal node is present, there is probably a metastatic chain of nodes along the course of the thoracic duct.

The lungs were involved in 78 per cent of cases. When there was pulmonary involvement the liver was affected in 75 per cent of the cases. The genitourinary tract was involved in 24 per cent of all cases. When there was pulmonary metastasis the mediastinal nodes were involved in 55 per cent of cases.

In nearly all of these cases there was bilateral involvement of the abdomen, either of the lymphatic glands or of intra-abdominal organs, namely, the liver, the kidneys or the spleen.

Counseller, Nichols and Smith [40] reported that up to the time of their report 47 cases of anorchia could be found in the literature; in 11 the condition was bilateral, and in 36, unilateral. Since 1931, when 2 cases

39. Barringer, B. S., and Earl, D.: Teratoma Testis: Survey of Thirty-Seven Autopsy Records, Surg., Gynec. & Obst. **72**:591-600 (March) 1941.

40. Counseller, V. S.; Nichols, D. R., and Smith, H. L.: Congenital Absence of Testis: A Report of Seven Cases of Monorchidism, J. Urol. **44**:237-241 (Aug.) 1940.

of bilateral anorchidism were observed at the Mayo Clinic and were reported by Counseller and Walker, 7 additional cases had been observed at the clinic. In these 7 cases each of the patients was 21 years of age or less. In all but 1 case a vas deferens was found. It was frequently necessary to open the peritoneum in order to exclude definitely the presence of a testis. In 4 of the 7 cases absence of the testis occurred on the left side and in 3 on the right.

Biopsy.—Charny [41] stated that testicular biopsy is a simple, innocuous procedure, basing his opinion on its application in the cases of 40 infertile patients without a single mishap. Testicular biopsy is not only a definite diagnostic aid in differentiating between obstructive and nonobstructive seminal defects but serves a prognostic function. When performed before and after treatment, testicular biopsy yields the most direct evidence of the efficiency of the therapeutic agent employed.

URETHRA

Infection.—Knight, Uhle and LaTowsky [42] reported a study of the results of sulfathiazole treatment of gonorrheal urethritis in the male. A total of 55 patients were studied, 50 of whom were followed to the completion of the study. Of the 50 patients followed, 96 per cent were cured by an average of eight days' treatment with an average dose of 28 Gm. of the drug. Toxic reactions occurred in only 11.5 per cent of the cases. The average time required for bacteriologic cure was twenty-eight days. The criteria of cure in this study were strict and included as the final provocative test two or more sterile smears and cultures of the prostatic fluid. Sulfathiazole was found to be a particularly valuable drug for the treatment of gonorrheal urethritis in the male, not only because of its therapeutic efficiency but because of the low incidence of toxic reactions encountered.

Gonococcic Infection.—Van Slyke, Wolcott and Mahoney [43] stated that there are obvious objections to the general use of sulfanilamide as an agent in the treatment of gonococcic infection.

Sulfapyridine was used in 300 cases of gonococcic infection. The rate of cure approximated 85 per cent for patients who had not received previous chemotherapy and 70 per cent for those who had failed to

41. Charny, C. W.: Testicular Biopsy: Its Value in Male Sterility, J. A. M. A. **115**:1429-1432 (Oct. 26) 1940.

42. Knight, F.; Uhle, C. A. W., and LaTowsky, L. W.: The Treatment of Gonorrheal Urethritis in the Male with Sulfathiazole, J. Urol. **44**:748-752 (Dec.) 1940.

43. Van Slyke, C. J.; Wolcott, R. R., and Mahoney, J. F.: The Chemotherapy of Gonococcic Infections: I. Summary of Experience with Sulfanilamide; II, Investigation of Chemotherapeutic Effect of Sulfapyridine, J. A. M. A. **116**:276-280 (Jan. 25) 1941.

benefit by earlier sulfanilamide treatment. Subclinical carrier states were not encountered among patients treated with sulfapyridine.

The larger doses (6 Gm. a day) were not more efficacious than the smaller ones (2 Gm. a day). Toxic responses were milder and less frequent in the patients who received the smaller doses.

Toxic manifestations were not serious and were significantly less than those resulting from administration of sulfanilamide.

Prolonged administration is not indicated. Sulfapyridine therapy should be limited to ten days or less.

Sound clinical judgment alone can serve as a practical guide to the use of sulfapyridine in the treatment of gonococcic infection if the lack of laboratory facilities would otherwise curtail the use of the drug. Treatment with sulfapyridine appears applicable to the comprehensive therapeutic needs of the disease.

Rupture.—Harrison [44] discussed the methods used in the treatment of 21 patients who had injuries of the urethra. Twelve of these had injury of the bulbous portion of the urethra. Nine patients had rupture of the membranous portion of the urethra as a result of fractures of the pelvic bones.

The best results for rupture of the bulbous portion have been obtained by immediate external urethrotomy, whereas the operative management of rupture of the membranous portion consists of a combined suprapubic and perineal approach, particularly when the rupture is accompanied with fracture of the pubis and ischium.

TORSION OF THE APPENDIX TESTIS

Scott [45] reported a case of torsion of the appendix testis and stated that this condition may account for many of the cases of so-called epididymo-orchitis occurring during childhood and adolescence. The treatment should always be surgical, as operation is without risk and recovery from conservative treatment requires more time than does recovery from surgical treatment.

URACHAL CALCULUS

Wyatt and Lanman [46] reported the finding of a calculus in the urachus of a white boy aged 7 years. The main difficulty experienced by the

44. Harrison, J. H.: The Treatment of Rupture of the Urethra, Especially When Accompanying Fractures of the Pelvic Bones, Surg., Gynec. & Obst. **72:** 622-631 (March) 1941.

45. Scott, R. T.: Torsion of the Appendix Testis, J. Urol. **44:**755-758 (Dec.) 1940.

46. Wyatt, G. M., and Lanman, T. H.: Calculus in Urachus: Report of Case with Enuresis, Am. J. Roentgenol. **43:**673-675 (May) 1940.

patient was incontinence. A roentgenogram showed a calculus in the upper region of the bladder. The stone was found embedded in the center of the mass, which was removed through a midline suprapubic incision. The diagnosis was calcification and ossification of a remnant of a urachal cyst. The patient recovered readily, and shortly after the operation his urinary control became normal.

SQUAMOUS CELL CHANGES IN THE URINARY TRACT

Scholl [47] stated that squamous cell changes of the mucous membrane lining the urinary tract are generally associated with infection and localized trauma. Two cases were reported in which there was evidence of long-standing urethral obstruction and infection of the urinary tract. In 1 case symptoms had been present for eleven years; in the other, for twenty-five years. In 1 of the cases reported there was an extensive squamous cell carcinoma which had deeply infiltrated most of the vesical wall. In the other case widespread leukoplakial areas were found in the mucous membrane of the bladder, the ureter and both renal pelves. Malignant changes were found in the vesical plaques.

Neither of the patients had received treatment for his urinary infection during the many years of what was possibly a premalignant period. It is probable that early institution of the usual methods of treatment would have diminished the extent of the urinary obstruction and infection and possibly would have arrested the process of metaplasia before it had advanced to an irreversible stage. Although leukoplakia and squamous cell carcinoma occur only rarely as complications of obstruction and infection, their possible occurrence is one more reason for continued effort by the members of the medical profession to reduce or eradicate these commonly seen and persistent infections of the urinary tract.

UROGRAPHY

Arendt and Maslow [48] stated that by filling the bladder with from 150 to 250 cc. of oil they were able to prevent intravenously injected dye from reaching the bladder, thus keeping it back in the ureters and pelves without need of any outside compression. They thus had (1) a more complete filling of the pelves and the calices; (2) less spastic and reflex contractions of the pelves and the ureters, and (3) a clear outline of the lower pelvic portions of the ureters, which are usually obscured by the

47. Scholl, A. J.: Squamous Cell Changes and Infection in the Urinary Tract, J. Urol. **44**:759-767 (Dec.) 1940.

48. Arendt, J., and Maslow, L. A.: Blocking of the Ureters in Intravenous Pyelography by Means of Filling the Bladder with Oil, Radiology **35**:350-352 (Sept.) 1940.

dye in the bladder. The procedure is simple and harmless when contraindications are observed.

Shiflett and Keith [49] stated that the lateral pyelogram has a wide range of usefulness. The technic is simple and does not appreciably delay the urologist or add to the discomfort of the patient. The normal variable is much less than in the average system, which makes it relatively easy to detect pathologic changes. It permits convincing topographic differentiation of intra-abdominal and retroperitoneal tumors and also differentiation of retroperitoneal lesions themselves and can be used to advantage in roentgen investigation of all problems relating to the urinary tract. Elective lateral pyelographic study is of as much value as the lateralization of any organ or system of organs other than the kidneys and should be placed on an equal plane.

Nichols [50] stated that he has been interested in lateral pyelography, particularly in the diagnosis and location of suspicious shadows in the region of the kidneys. Often dense shadows which appear to be calculi lost in the pyelographic medium on an anteroposterior exposure are found, when a pyelogram is made, to be shadows either posterior or anterior to the kidney. Therefore, Nichols employs lateral pyelograms almost routinely when renal calculi are suspected if they are not definitely identified by either a pyelogram or an excretory urogram. Nichols stated that he also finds this procedure a valuable adjunct to examination for suspected perinephritic abscess.

STERILITY

Kreutzmann [51] stated that all cases of sterility in the male can be divided into two groups, urologic and endocrinologic. In the urologic cases the condition is either congenital or acquired.

At present it is only in cases of hypothyroidism that consistently good results are obtained. The administration of large doses of testosterone propionate causes marked decrease in the number of spermatozoa per cubic centimeter. The injection of 5 mg. of testosterone propionate three times a week for one month caused no appreciable change in the percentage of abnormal forms in patients with either normal or abnormal sperm counts. Repeated sperm analyses should be made during treatment to guard against transient or possible permanent damage to the spermatogenic structures of the individual patient.

---

49. Shiflett, E. L., and Keith, D. Y.: Lateral Pyelography, Am. J. Roentgenol. **43**:664-671 (May) 1940.

50. Nichols, B. H., in discussion on Shiflett and Keith.[49]

51. Kreutzmann, H. A. R.: Sterility in the Male: Diagnosis and Treatment, J. A. M. A. **115**:1424-1426 (Oct. 26) 1940.

(To Be Concluded)

News and Comment

Statement Concerning the New "Progress in Orthopedic Surgery."—"Progress in Orthopedic Surgery" is now sponsored by the American Academy of Orthopaedic Surgeons and is being prepared under the direction of its editorial committee. It is to be published only once a year and will include a survey of the literature for the preceding year. An editorial board of twenty-two orthopedic surgeons, representing twenty-one clinics from all sections of the country, has been appointed. The chairman of this editorial board has selected from the *Quarterly Cumulative Index Medicus* of 1940 the titles of 1,793 articles of orthopedic interest. Each editor has been assigned a subject, to which in most instances either he or the clinic he represents has made definite contributions in the past. The assistance of many younger men in these clinics and of others has been used in the preparation of the material. Only those articles which appear to the editor preparing the section to represent definite progress or to be of unusual interest and to warrant attention have been used in the final proof. This new "Progress" will be from two to three times as large as the total size of the former reports and will contain about 80,000 words, representing about 750 articles.

The following are the 20 sections of the "Progress," each prepared by a separate editor:

1. Congenital Dislocation of the Hip
2. Other Congenital Deformities
3. Diseases of Growing and Adult Bone
4. Tuberculosis of Bones and Joints
5. Infections of Bones and Joints, Exclusive of Tuberculosis
6. Chronic Arthritis
7. Infantile Paralysis
8. Neuromuscular Disorders, Exclusive of Infantile Paralysis
9. Fresh Fractures and Dislocations
10. Fracture Deformities
11. Bone Tumors
12. Diseases Low in the Back
13. Diseases of the Spine, Exclusive of Those Low in the Back
14. Diseases of the Hip
15. Diseases of the Knee
16. Diseases of the Foot and Ankle
17. Diseases of the Shoulder, Neck and Jaw
18. Diseases of the Elbow, Forearm, Wrist and Hand
19. Apparatus, Technic and Amputations
20. Research